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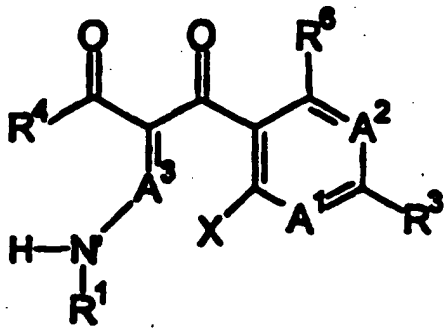
(54) Title: PROCESS FOR MAKING QUINOLONYL LACTAM ANTIMICROBIALS AND NOVEL INTERMEDIATE COMPOUNDS

(57) Abstract

The present invention provides processes for making compounds of the structure (Q-L^1)-L-(L^2-B), wherein (I) Q is a quinolone moiety; (II) B is a lactam moiety; and (III) L, L^1, and L^2 together comprise a linking moiety; comprising the steps of: (1) coupling a compound of formula (III) with a lactam-containing compound to form an intermediate compound; and (2) cyclizing the intermediate by reaction with an organosilicon compound to give a compound of the formula (Q-L^1)-L-(L^2-B). Preferably, the process additionally comprises a step prior to the coupling step, wherein protected forms of the compound of formula (III) and the lactam compound are formed; and deprotection steps after the cyclization step, wherein the protecting groups are removed. Preferred antimicrobial compounds made by these processes are those where the beta-lactam moiety is a penem, a carbapenem, a cephem, or a carbacephem. Also preferred are those compounds where L^1, L, and L^2 form a carbamate moiety, or a secondary or tertiary amine moiety. The present invention also provides novel intermediate compounds of the formula (M-L^1)-L-(L^2-B), where (I) M has a structure according to formula (IV), (II) B is a lactam moiety, and (III) L, L^1, and L^2 together comprise a linking moiety.



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PROCESS FOR MAKING QUINOLONYL LACTAM ANTIMICROBIALS AND NOVEL INTERMEDIATE COMPOUNDS

BACKGROUND OF THE INVENTION

This invention relates to processes for making antimicrobial compounds. The compounds made by this invention contain, as integral substituents, a quinolone moiety and a lactam-containing moiety. The invention further relates to novel intermediate compounds that are useful in making the antimicrobial compounds.

The chemical and medical literature describes a myriad of compounds that are said to be antimicrobial, i.e., capable of destroying or suppressing the growth or reproduction of microorganisms, such as bacteria. In particular, antibacterials include a large variety of naturally-occurring (antibiotic), synthetic, or semi-synthetic compounds. They may be classified (for example) as the aminoglycosides, ansamacrolides, beta-lactams (including penicillins and cephalosporins), lincosaminides, macrolides, nitrofurans, nucleosides, oligosaccharides, peptides and polypeptides, phenazines, polyenes, polyethers, quinolones, tetracyclines, and sulfonamides. Such antibacterials and other antimicrobials are described in Antibiotics, Chemotherapeutics, and Antibacterial Agents for Disease Control (M. Grayson, editor, 1982), and E. Gale et al., The Molecular Basis of Antibiotic Action 2d edition (1981), both incorporated by reference herein.

Recently, a new class of highly potent, broad spectrum antimicrobials was discovered, combining beta-lactam moieties with quinolone moieties. These compounds have been referred to as "Quinolonyl Lactam Antimicrobials" (herein referred to as "QLAs)." Such compounds are described in European Patent Publication 366,189, White and Demuth, published May 2, 1990; European Patent Publication 366,193, Demuth and White, published May 2, 1990; European Patent Publication 366,640, Demuth and White, published May 2, 1990; and European Patent Publication 366,641, White and Demuth, published May 2, 1990. Other such compounds are described in Australian Patent Publication 87/75009, Albrecht et al., published January 7, 1988; Australian Patent Publication 88/27554, published June 6, 1989; European Patent Publication 335, 297, Albrecht et al., published October 4, 1989; and Albrecht et al., "Dual-Action Cephalosporins: Cephalosporin 3'-Quinolone Carbamates", 34 J. Medicinal Chemistry 2857 (1991).

Manufacture of QLAs generally involves synthesis of suitably protected substituent beta-lactam and quinolone moieties, a linking process, and appropriate

de-protection steps. The specific linking process depends, of course, on the specific lactam and quinolone substituent moieties used, as well as the type of linkage desired. Several such linking processes have been described in the literature. However, the overall yields of these processes are sometimes low, due in part to degradation caused by the use of harsh reagents and polar solvents (e.g., water), and to poor solubility of the components in organic solvents, particularly the quinolone or related heterocyclic component. Additionally, the linking processes known in the art offer limited synthetic flexibility.

It has now been discovered that linking processes which employ a quinolone precursor and, optionally, utilize organosilicon compounds in the linking step are useful in making QLAs. Such processes surprisingly allow efficient synthesis of QLA precursors under reaction conditions that provide good solubility of the quinolone precursor or related heterocyclic component, and do not use the harsh reagents and polar solvents taught by the prior art. Sensitive functional groups in the reaction substrate and product tolerate these mild reaction conditi ns. Additionally, these processes are particularly useful when used in conjunction with the ring closure methodology for quinolones and related heterocyclic moieties, specifically described and claimed in co-pending application Serial No.___, filed August 2, by Randall et al. The mild reaction conditions of these processes may allow for improved QLA yields and purities, and provide the synthetic flexibility to make QLAs that, if prepared utilizing the prior art, might be accessable only in low to moderate yields.

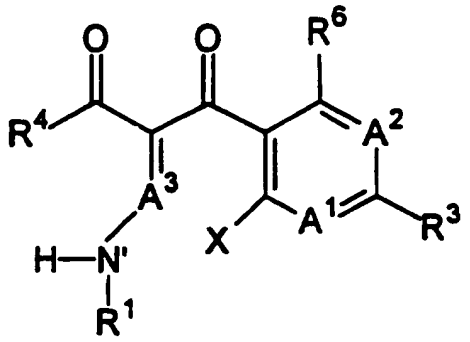
SUMMARY OF THE INVENTION

The present invention provides methods of making a compound of the formula

$$(Q - L^1) - L - (L^2 - B)$$

the method comprising the steps of:

(1) coupling a compound having a structure according to Formula (III)



(III)

wherein

(A) (1) A^1 is N or $C(R^7)$; where

(a) R^7 is hydrogen, hydroxy, alkoxy, nitro, cyano, halogen, alkyl, or $-N(R^8)(R^9)$, and

(b) R^8 and R^9 are, independently, hydrogen, alkyl, alkenyl, a carbocyclic ring, or a heterocyclic ring; or R^8 and R^9 together comprise a heterocyclic ring including the nitrogen to which they are bonded;

(2) A^2 is N or $C(R^2)$; where R^2 is hydrogen or halogen;

(3) A^3 is N or $C(R^5)$; where R^5 is hydrogen;

(4) R^1 is hydrogen, alkyl, a carbocyclic ring, a heterocyclic ring, alkoxy, hydroxy, alkenyl, arylalkyl, or $-N(R^8)(R^9)$;

(5) R^3 is hydrogen, halogen, alkyl, a carbocyclic ring, or a heterocyclic ring;

(6) R^4 is hydroxy;

(7) R^6 is hydrogen, halogen, nitro, hydrazino or $-N(R^8)(R^9)$; and

(8) X is a leaving group

(B) and

(1) when A^2 is $C(R^2)$, R^2 and R^3 may together comprise $-O-(CH_2)_n-O-$, where n is from 1 to 4;

(2) when A^3 is $C(R^5)$, R^4 and R^5 may together comprise a heterocyclic ring; and

(3) when A^1 is $C(R^7)$, R^7 and R^3 may together comprise a heterocyclic ring including A^1 and the carbon atom to which R^3 is bonded;

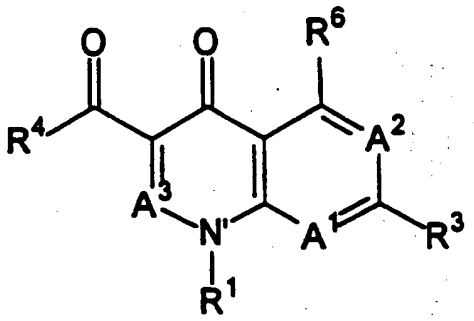
or a protected form, salt, ester, or solvate thereof;

with a lactam-containing compound having a structure according to Formula (II), to form an intermediate compound; and

(2) cyclizing the intermediate compound by reaction with an organosilicon compound to give a compound of the formula $(Q - L^1) - L - (L^2 - B)$;

wherein

(I) Q has a structure according to Formula (I)



(I)

wherein

(A) (1) A^1 is N or $C(R^7)$; where

(a) R^7 is hydrogen, hydroxy, alkoxy, nitro, cyano, halogen, alkyl, or $-N(R^8)(R^9)$, and

(b) R^8 and R^9 are, independently, R^{8a} where R^{8a} is hydrogen, alkyl, alkenyl, a carbocyclic ring, or a heterocyclic ring; or R^8 and R^9 together comprise a heterocyclic ring including the nitrogen to which they are bonded;

(2) A^2 is N or $C(R^2)$; where R^2 is hydrogen or halogen;

(3) A^3 is N or $C(R^5)$; where R^5 is hydrogen;

(4) R^1 is hydrogen, alkyl, a carbocyclic ring, a heterocyclic ring, alkoxy, hydroxy, alkenyl, arylalkyl, or $-N(R^8)(R^9)$;

(5) R^3 is hydrogen, halogen, alkyl, a carbocyclic ring, or a heterocyclic ring;

(6) R^4 is hydroxy; and

(7) R^6 is hydrogen, halogen, nitro, hydrazino or $-N(R^8)(R^9)$;

(B) and

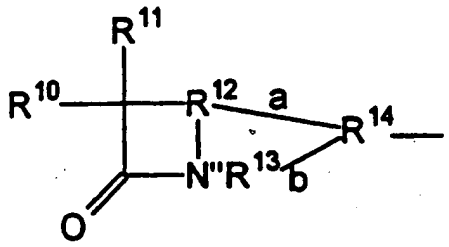
(1) when A^2 is $C(R^2)$, R^2 and R^3 may together comprise $-O-(CH_2)_n-O-$, where n is from 1 to 4;

(2) when A^3 is $C(R^5)$, R^4 and R^5 may together comprise a heterocyclic ring; and

(3) when A^1 is $C(R^7)$, R^7 and R^3 may together comprise a heterocyclic ring including A^1 and the carbon at m t which R^3 is bonded;

(C) and provided that one f R^1, R^3, or R^6 is a covalent bond to L^1;

(II) B has a structure according to Formula (II):



(II)

wherein

(A) R^{10} is hydrogen, halogen, alkyl, alkenyl, heteroalkyl, a carbocyclic ring, a heterocyclic ring, R^8-O-, R^8CH=N-, $(R^8)(R^9)$N-, R^{17}-C(=CHR^{20})-C(=O)NH-, R^{17}-C(=NO-R^{19})-C(=O)NH-, or R^{18}-$(CH_2)_m$-C(=O)NH-; where

(1) m is an integer from 0 to 9;

(2) R^{17} is hydrogen, alkyl, alkenyl, heteroalkyl, heteroalkenyl, a carbocyclic ring, or a heterocyclic ring;

(3) R^{18} is R^{17}, -Y^1, or -CH(Y^2)(R^{17});

(4) R^{19} is R^{17}, arylalkyl, heteroarylalkyl,-C(R^{22})(R^{23})-COOH, -C(=O)O-R^{17}, or -C(=O)NH-R^{17}, where R^{22} and R^{23} are, independently, R^{17} or together comprise a carbocyclic ring or a heterocyclic ring including the carbon atom to which R^{22} and R^{23} are bonded;

(5) R^{20} is R^{19}, halogen, -Y^1, or -CH(Y^2)(R^{17});

(6) Y^1 is -C(=O)OR^{21}, -C(=O)R^{21}, -N(R^{24})R^{21}, -$S(O)_p$ R^{29}, or -OR^{29}; and Y^2 is Y^1 or -OH, -SH, or -SO_3H;

(a) p is an integer from 0 to 2;

(b) R^{24} is hydrogen; alkyl; alkenyl; heteroalkyl; heteroalkenyl; a carbocyclic ring; a heterocyclic ring; -SO_3H; -C(=O)R^{25}; or, when R^{18} is -CH(N(R^{24})R^{21})(R^{17}), R^{24} may comprise a moiety bonded to R^{21} to form a heterocyclic ring; and

(c) R^{25} is R^{17}, NH(R^{17}), N(R^{17})(R^{26}), O(R^{26}), or S(R^{26}); where R^{26} is alkyl, alkenyl, a carb cyclic ring, a heterocyclic ring, or when R^{25} is -N(R^{17})(R^{26}), R^{26} may

be a moiety bonded to R^{17} to form a heterocyclic ring; and

(7) R^{21} is R^{29} or hydrogen; where R^{29} is alkyl; alkenyl; arylalkyl; heteroalkyl; heteroalkenyl; heteroarylalkyl; a carbocyclic ring; a heterocyclic ring; or, when Y is -$N(R^{24})R^{21}$ and R^{21} is R^{29}, R^{21} and R^{24} may together comprise a heterocyclic ring including the nitrogen atom to which R^{24} is bonded;

(B) R^{11} is hydrogen, halogen, alkoxy, or $R^{27}C(=O)NH$-, where R^{27} is hydrogen or alkyl;

(C) bond "a" is a single bond or is nil; and bond "b" is a single bond, a double bond, or is nil; except bond "a" and bond "b" are not both nil;

(D) R^{12} is -$C(R^8)$-, or -CH_2-R^{28}-; where R^{28} is -$C(R^8)$, -O-, or -N-, and R^{28} is directly bonded to N" in Formula (II) to form a 5-membered ring;

except, if bond "a" is nil, then R^{12} is

(1) -$C(R^8)(X^1)$-, where

(a) X^1 is -R^{21}; -OR^{30}; -$S(O)_rR^{30}$, where r is an integer from 0 to 2; -$OC(=O)R^{30}$; r -$N(R^{30})R^{31}$; and

(b) R^{30} and R^{31} are, independently, alkyl, alkenyl, a carbocyclic ring or a heterocyclic ring; or R^{30} and R^{31} together comprise a heterocyclic ring including the nitrogen at m to which R^{30} and R^{31} are bonded; or

(2) -CH_2-R^{32}-; where R^{32} is -$C(R^8)(R^{21})$, -O-, or -NR^8, and R^{32} is directly bonded to N" in Formula (II) to form a 5-membered ring;

(E) (1) if bond "b" is a single bond, R^{13} is -$CH(R^{33})$; r, -$C(O)NHSO_2$-, if bond "a" is nil; or -$C^*(R^{33})$- if R^{14} contains a R^{36} moiety; where R^{33} is hydr gen or $COOR^{46}$ where R^{46} is hydrogen, alkyl or alkenyl, and C* is linked to R^{36} t f rm a 3-membered ring;

(2) if bond "b" is a double bond, R^{13} is -$C(R^{33})$=; or

(3) if bond "b" is nil, R^{13} is hydrogen, -SO_3H, -$PO(OR^{34})OH$, -$C(O)NHSO_2N(R^{34})(R^{35})$,

$-OSO_3H$, $-CH(R^{35})COOH$, or $-OCH(R^{34})-COOH$; where R^{34} is hydrogen, alkyl, alkenyl, a carbocyclic ring, or a heterocyclic ring; and R^{35} is hydrogen, alkyl, alkenyl, or $-NHR^8$; or, if R^{13} is $-C(O)NH-SO_2N-(R^{34})(R^{35})$, R^{34} and R^{35} may together comprise a heterocyclic ring including the nitrogen t which R^{34} and R^{35} are bonded; and

(F) (1) if bond "a" or bond "b" is nil, then R^{14} is a covalent bond;

(2) if bond "a" and "b" are single bonds, R^{14} is $-W-C'''=C(R^{8a})-R^{37}-$, or $-W-C'''(R^{36})-R^{37}-$; or

(3) if bond "a" is a single bond and bond "b" is a double bond, R^{14} is $-C(R^8)(R^{38})-W-C'''-R^{37}-$; $-W-C(R^8)-(R^{38})-C'''-R^{37}-$; or $-W-C'''-R^{37}-$;

(4) where

(a) W is O; $S(O)_s$, where s is an integer from 0 to 2; or $C(R^{38})$, where R^{38} is hydrogen, alkyl or alkoxy;

(b) R^{36} is hydrogen; alkyl; alkenyl; -COOH; or, if R^{13} is $-C^*(R^{33})$, R^{36} may be linked to C^* t form a 3-membered carbocyclic ring;

(c) R^{37} is covalent bond, alkyl, alkenyl, a carbocyclic ring, or a heterocyclic ring; and

(d) C''' is directly bonded to R^{13} to form a 5- or 6-membered ring; and

(III) (A) L is $-C(=Z)-$; $-S(O)_v-$; $-N(R^{44})-$; $-N^+(R^{44})(R^{45})-$; $-N(R^{44})-N(R^{44})-$; -O-; =N-; or a covalent bond; and L is bonded to L^3 and L^4; where

(1) Z is O, S, or $^+N(H)_2$;

(2) v is 0, 1 or 2;

(3) R^{44} is hydrogen, substituted or unsubstituted lower alkyl, aryl, acyl, hydroxy, alkoxy, aryloxy, or acyloxy; and

(4) R^{45} is hydrogen, unsubstituted or substituted lower alkyl, or substituted or unsubstituted aryl;

(B) L^1 is L^3 or $R^{15}L^3$; where

(1) when L is $-C(=Z)-$, L^3 is a covalent bond, oxygen, sulfur, or nitrogen; and when L is other than $-C(=Z)-$,

L^3 is a covalent bond;

(2) R^{15} is alkyl, alkenyl, heteroalkyl, a heterocyclic ring, a carbocyclic ring, or R^{15} together with L^3 is a heteroalkyl or a heterocyclic ring; and

(3) L^1 is bonded to Q at the point of attachment of R^1, R^3 or R^6, whichever is a covalent bond;

(C) L^2 is L^4, $-X^2_t-R^{39}-L^4$, or $-X^3_t-R^{39}-L^4$; where

(1) when L is -C(=Z)-, L^4 is a covalent bond, oxygen, sulfur, or nitrogen; and when L is other than -C(=Z)-, L^4 is a covalent bond;

(2) X^2 is oxygen, or $S(O)_v$, where v is 0, 1, or 2;

(3) X^3 is nitrogen; $-N(R^{40})-$; $-N^+(R^{41})(R^{42})-$; or R^{43}-$N(R^{41})$; and is linked to R^{14} by a single or double bond; or, if R^{14} is covalent bond, X^3 is linked to B by a single or double bond; where

(a) R^{40} is R^8; $-OR^8$; or $-C(=O)R^8$;

(b) R^{41} and R^{42} are, independently, hydrogen; alkyl; alkenyl; carbocyclic rings; heterocyclic rings; or, if R^6 is $R^{16}X$, then R^{41} and R^{42} together with "Q" may comprise a heterocyclic ring as R^{16};

(c) R^{43} is $N(R^{41})$, oxygen or sulfur;

(4) t is 0 or 1;

(5) R^{39} is alkyl, alkenyl, heteroalkyl, heteroalkenyl, a carbocyclic ring, or a heterocyclic ring; and

(6) (a) if bond "a" or bond "b" is nil, then L^2 is bonded directly to R^{12} or R^{13}; or

(b) if bond "a" and bond "b" are not nil, then L^2 is bonded to R^{14};

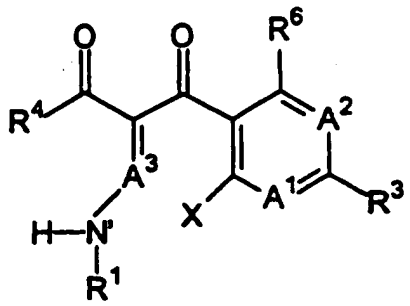
(D) provided that if L^1, L^2 and R^{37} are each a covalent bond, then L cannot be a covalent bond;

or a protected form, salt, pharmaceutically-acceptable salt, biohydrolyzable ester, or solvate thereof.

The present invention further relates to a process for making an intermediate compound having a structure according the formula

$$(M - L^1) - L - (L^2 - B)$$

the method comprising the coupling of a compound having a structure according t F rmula (III)



(III)

wherein

(A) (1) A^1 is N or $C(R^7)$; where

(a) R^7 is hydrogen, hydroxy, alkoxy, nitro, cyano, halogen, alkyl, or $-N(R^8)(R^9)$, and

(b) R^8 and R^9 are, independently, hydrogen, alkyl, alkenyl, a carbocyclic ring, or a heterocyclic ring; or R^8 and R^9 together comprise a heterocyclic ring including the nitrogen to which they are bonded;

(2) A^2 is N or $C(R^2)$; where R^2 is hydrogen or halogen;

(3) A^3 is N or $C(R^5)$; where R^5 is hydrogen;

(4) R^1 is hydrogen, alkyl, a carbocyclic ring, a heterocyclic ring, alkoxy, hydroxy, alkenyl, arylalkyl, or $-N(R^8)(R^9)$;

(5) R^3 is hydrogen, halogen, alkyl, a carbocyclic ring, or a heterocyclic ring;

(6) R^4 is hydroxy;

(7) R^6 is hydrogen, halogen, nitro, hydrazino or $-N(R^8)(R^9)$; and

(8) X is a leaving group

(B) and

(1) when A^2 is $C(R^2)$, R^2 and R^3 may together comprise $-O-(CH_2)_n-O-$, where n is from 1 to 4;

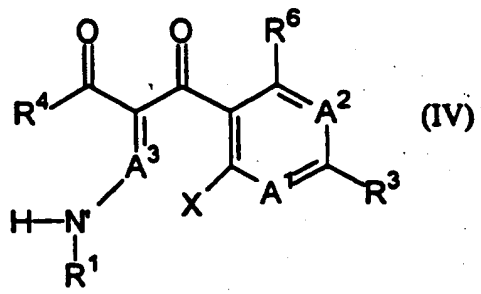
(2) when A^3 is $C(R^5)$, R^4 and R^5 may together comprise a heterocyclic ring; and

(3) when A^1 is $C(R^7)$, R^7 and R^3 may t gether comprise a heterocyclic ring including A^1 and the carbon atom to which R^3 is bonded;

or a protected form, salt, ester, or solvate thereof;
with a lactam-containing compound having a structure according to Formula (II)

wherein

(I) M has a structure according to Formula (IV)



(IV)

wherein

(A) (1) A^1 is N or $C(R^7)$; where

(a) R^7 is hydrogen, hydroxy, alkoxy, nitro, cyano, halogen, alkyl, or $-N(R^8)(R^9)$, and

(b) R^8 and R^9 are, independently, R^{8a} where R^{8a} is hydrogen, alkyl, alkenyl, a carbocyclic ring, or a heterocyclic ring; or R^8 and R^9 together comprise a heterocyclic ring including the nitrogen to which they are bonded;

(2) A^2 is N or $C(R^2)$; where R^2 is hydrogen or halogen;

(3) A^3 is N or $C(R^5)$; where R^5 is hydrogen;

(4) R^1 is hydrogen, alkyl, a carbocyclic ring, a heterocyclic ring, alkoxy, hydroxy, alkenyl, arylalkyl, or $-N(R^8)(R^9)$;

(5) R^3 is hydrogen, halogen, alkyl, a carbocyclic ring, or a heterocyclic ring;

(6) R^4 is hydroxy;

(7) R^6 is hydrogen, halogen, nitro, hydrazin , r $-N(R^8)(R^9)$; and

(8) X is a leaving group;

(B) and

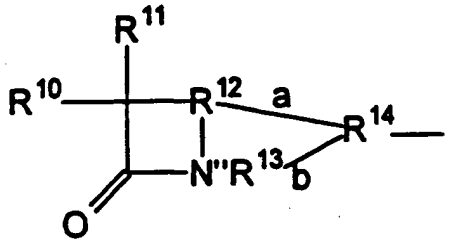
(1) when A^2 is $C(R^2)$, R^2 and R^3 may together comprise $-O-(CH_2)_n-O-$, where n is fr m 1 to 4;

(2) when A^3 is $C(R^5)$, R^4 and R^5 may together comprise a het rocyclic ring; and

(3) when A^1 is $C(R^7)$, R^7 and R^3 may together comprise a heterocyclic ring including A^1 and the carbon atom to which R^3 is bonded;

(C) and provided that one of R^1, R^3, or R^6 is a covalent bond t L^1;

(II) B has a structure according to Formula (II):



(II)

wherein

(A) R^{10} is hydrogen, halogen, alkyl, alkenyl, heteroalkyl, a carbocyclic ring, a heterocyclic ring, R^8-O-, R^8CH=N-, $(R^8)(R^9)$N-, R^{17}-C(=CHR^{20})-C(=O)NH-, R^{17}-C(=NO-R^{19})-C(=O)NH-, or R^{18}-$(CH_2)_m$-C(=O)NH-; where

(1) m is an integer from 0 to 9;

(2) R^{17} is hydrogen, alkyl, alkenyl, heteroalkyl, heteroalkenyl, a carbocyclic ring, or a heterocyclic ring;

(3) R^{18} is R^{17}, -Y^1, or -CH(Y^2)(R^{17});

(4) R^{19} is R^{17}, arylalkyl, heteroarylalkyl, -C(R^{22})-(R^{23})-COOH, -C(=O)O-R^{17}, or -C(=O)NH-R^{17}, where R^{22} and R^{23} are, independently, R^{17} or together comprise a carbocyclic ring or a heterocyclic ring including the carbon atom to which R^{22} and R^{23} are bonded;

(5) R^{20} is R^{19}, halogen, -Y^1, or -CH(Y^2)(R^{17});

(6) Y^1 is -C(=O)OR^{21}, -C(=O)R^{21}, -N(R^{24})R^{21}, -$S(O)_p$ R^{29}, or -OR^{29}; and Y^2 is Y^1 or -OH, -SH, or -SO_3H;

(a) p is an integer from 0 to 2;

(b) R^{24} is hydrogen; alkyl; alkenyl; heteroalkyl; heteroalkenyl; a carbocyclic ring; a heterocyclic ring; -SO_3H; -C(=O)R^{25}; r, when R^{18} is -CH(N(R^{24})R^{21})(R^{17}), R^{24}

may comprise a moiety bonded to R^{21} to form a heterocyclic ring; and

(c) R^{25} is R^{17}, $-NH(R^{17})$, $-N(R^{17})(R^{26})$, $O(R^{26})$, or $S(R^{26})$; where R^{26} is alkyl, alkenyl, a carbocyclic ring, a heterocyclic ring, or when R^{25} is $-N(R^{17})(R^{26})$, R^{26} may be a moiety bonded to R^{17} to form a heterocyclic ring; and

(7) R^{21} is R^{29} or hydrogen; where R^{29} is alkyl; alkenyl; arylalkyl; heteroalkyl; heteroalkenyl; heteroarylalkyl; a carbocyclic ring; a heterocyclic ring; or, when Y is $N(R^{24})R^{21}$ and R^{21} is R^{29}, R^{21} and R^{24} may together comprise a heterocyclic ring including the nitrogen atom to which R^{24} is bonded;

(B) R^{11} is hydrogen, halogen, alkoxy, or $R^{27}C(=O)NH-$, where R^{27} is hydrogen or alkyl;

(C) bond "a" is a single bond or is nil; and bond "b" is a single bond, a double bond, or is nil; except bond "a" and bond "b" are not both nil;

(D) R^{12} is $-C(R^8)-$, or $-CH_2-R^{28}-$; where R^{28} is $-C(R^8)-$, -O-, or -N-, and R^{28} is directly bonded to N" in Formula (II) t form a 5-membered ring;

except, if bond "a" is nil, then R^{12} is

(1) $-C(R^8)(X^1)-$, where

(a) X^1 is $-R^{21}$; $-OR^{30}$; $-S(O)_rR^{30}$, where r is an integer from 0 to 2; $-OC(=O)R^{30}$; or $N(R^{30})R^{31}$; and

(b) R^{30} and R^{31} are, independently, alkyl, alkenyl, a carbocyclic ring or a heterocyclic ring; or R^{30} and R^{31} together comprise a heterocyclic ring including the nitrogen atom to which R^{30} and R^{31} are bonded; or

(2) $-CH_2-R^{32}-$; where R^{32} is $-C(R^8)(R^{21})$, -O-, or $-NR^8$, and R^{32} is directly bonded to N" in Formula (II) to form a 5-membered ring;

(E) (1) if bond "b" is a single bond, R^{13} is $-CH(R^{33})$; or, $-C(O)NHSO_2-$, if bond "a" is nil; r $-C^*(R^{33})-$ if R^{14} contains a R^{36} moiety; where R^{33} is hydrogen

or $COOR^{46}$, where R^{46} is hydrogen, alkyl r alkenyl, and C* is linked t R^{36} to form a 3-membered ring;

(2) if bond "b" is a double bond, R^{13} is $-C(R^{33})=$; or

(3) if bond "b" is nil, R^{13} is hydrogen, $-SO_3H$, $-PO(OR^{34})OH$, $-C(O)NHSO_2N(R^{34})(R^{35})$, $-OSO_3H$, $-CH(R^{35})COOH$, or $-OCH(R^{34})-COOH$; where R^{34} is hydrogen, alkyl, alkenyl, a carbocyclic ring, or a heterocyclic ring; and R^{35} is hydrogen, alkyl, alkenyl, or $-NHR^8$; or, if R^{13} is $-C(O)NHSO_2N-(R^{34})(R^{35})$, R^{34} and R^{35} may together comprise a heterocyclic ring including the nitrogen to which R^{34} and R^{35} are bonded; and

(F) (1) if bond "a" or bond "b" is nil, then R^{14} is covalent bond;

(2) if bond "a" and "b" are single bonds, R^{14} is $-W-C'''=C(R^8)-R^{37}-$, or $-W-C'''(R^{36})-R^{37}-$; or

(3) if bond "a" is a single bond and bond "b" is a double bond, R^{14} is $-C(R^8)(R^{38})-W-C'''-R^{37}-$; $-W-C(R^8)-(R^{38})-C'''-R^{37}-$; or $-W-C'''-R^{37}-$;

(4) where

(a) W is O; $S(O)_s$, where s is an integer from 0 to 2; or $C(R^{38})$, where R^{38} is hydrogen, alkyl or alkoxy;

(b) R^{36} is hydrogen; alkyl; alkenyl; -COOH; or, if R^{13} is $-C^*(R^{33})$, R^{36} may be linked to C* t form a 3-membered carbocyclic ring;

(c) R^{37} is covalent bond, alkyl, alkenyl, a carbocyclic ring, or a heterocyclic ring; and

(d) C''' is directly bonded to R^{13} to form a 5- r 6-membered ring; and

(III) (A) L is $-C(=Z)-$; $-S(O)_v-$; $-N(R^{44})-$; $-N^+(R^{44})(R^{45})$; $-N(R^{44})-N(R^{44})-$; $-O-$; $=N-$; or a covalent bond; and L is bonded to L^3 and L^4; where

(1) Z is O, S, or $^+N(H)_2$;

(2) v is 0, 1 or 2;

(3) R^{44} is hydrogen, substituted or unsubstituted lower alkyl, aryl, acyl, hydroxy, alkoxy, aryloxy, or acyloxy;

and

(4) R^{45} is hydrogen, unsubstituted or substituted lower alkyl, or substituted or unsubstituted aryl;

(B) L^1 is L^3 or $R^{15}L^3$; where

(1) when L is -C(=Z)-, L^3 is a covalent bond, oxygen, sulfur, or nitrogen; and when L is other than -C(=Z)-, L^3 is a covalent bond;

(2) R^{15} is alkyl, alkenyl, heteroalkyl, a heterocyclic ring, a carbocyclic ring, or R^{15} together with L^3 is a heteroalkyl or a heterocyclic ring; and

(3) L^1 is bonded to Q at the point of attachment of R^1, R^3 or R^6, whichever is a covalent bond;

(C) L^2 is L^4, $-X^2_t-R^{39}-L^4$, or $-X^3_t-R^{39}-L^4$; where

(1) when L is -C(=Z)-, L^4 is a covalent bond, oxygen, sulfur, or nitrogen; and when L is other than -C(=Z)-, L^4 is a covalent bond;

(2) X^2 is oxygen, or $S(O)_v$, where v is 0, 1, or 2;

(3) X^3 is nitrogen; $N(R^{40})$; $N^+(R^{41})(R^{42})$; or R^{43}-$N(R^{41})$; and is linked to R^{14} by a single or double bond; or, if R^{14} is covalent bond, X^3 is linked t B by a single or double bond; where

(a) R^{40} is R^8; $-OR^8$; or $-C(=O)R^8$;

(b) R^{41} and R^{42} are, independently, hydrogen; alkyl; alkenyl; carbocyclic rings; heterocyclic rings; or, if R^6 is $R^{16}X$, then R^{41} and R^{42} together with Q" may comprise a heterocyclic ring as R^{16};

(c) R^{43} is $N(R^{41})$, oxygen or sulfur;

(4) t is 0 or 1;

(5) R^{39} is alkyl, alkenyl, heteroalkyl, heteroalkenyl, a carbocyclic ring, or a heterocyclic ring; and

(6) (a) if bond "a" or bond "b" is nil, then L^2 is bonded directly to R^{12} or R^{13}; or

(b) if bond "a" and bond "b" are not nil, then L^2 is bonded to R^{14};

(D) provided that if L^1, L^2 and R^{37} is each a covalent bond, then L is not a covalent b nd;

or a protected form, salt, ester, or s lvate thereof.

The present invention further relates to the intermediate lactam compounds of the formula (M - L^1) - L - (L^2 - B), wherein M, L^1, L, L^2 and B are as described hereinbefore. These intermediates are preferably prepared according to the processes of the present invention.

DESCRIPTION OF THE INVENTION

The present invention encompasses methods for making QLAs. The invention further encompasses novel compounds which are useful as intermediates for making QLAs. The QLAs made by the methods of the present invention are useful for treating infectious disorders in humans or other animal subjects. Thus, these QLAs must be pharmaceutically acceptable. As used herein, such a "pharmaceutically-acceptable" component is one that is suitable for use with humans and/or animals without undue adverse side effects (such as toxicity, irritation, and allergic response) commensurate with a reasonable benefit/risk ratio.

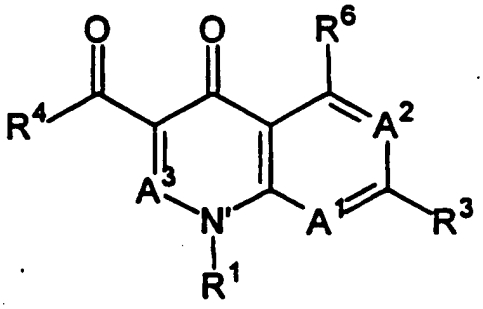
QLAs

The antimicrobial compounds ("QLAs") made by the methods of this invention encompass any of a variety of lactam moieties linked, by a linking moiety, to a quinolone moiety at the 1-, 5-, or 7-position of the quinolone. These compounds include those having a structure according to the general formula

$$(Q - L^1) - L - (L^2 - B)$$

wherein

(I) Q has a structure according to Formula (I)



(I)

wherein

(A) (1) A^1 is N or C(R^7); where

(a) R^7 is hydrogen, hydroxy, alkoxy, nitro, cyano, halogen, alkyl, or -N(R^8)(R^9) (preferably hydrogen or halogen), and

(b) R^8 and R^9 are, independently, R^{8a} where R^{8a} is hydrogen, alkyl, alkenyl, a carbocyclic ring, or a heterocyclic ring; or R^8 and R^9 together

comprise a heterocyclic ring including the nitrogen to which they are bonded;

(2) A^2 is N or (preferably) $C(R^2)$; where R^2 is hydrogen or halogen;

(3) A^3 is N or (preferably) $C(R^5)$; where R^5 is hydrogen;

(4) R^1 is hydrogen, alkyl, a carbocyclic ring, a heterocyclic ring, alkoxy, hydroxy, alkenyl, arylalkyl, or $-N(R^8)(R^9)$ (preferably alkyl or a carbocyclic ring);

(5) R^3 is hydrogen, halogen, alkyl, a carbocyclic ring, or a heterocyclic ring (preferably a heterocyclic ring);

(6) R^4 is hydroxy; and

(7) R^6 is hydrogen, halogen, nitro, hydrazino or $-N(R^8)(R^9)$;

(B) and

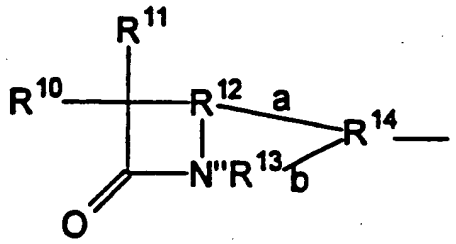
(1) when A^2 is $C(R^2)$, R^2 and R^3 may together comprise $-O-(CH_2)_n-O-$, where n is from 1 to 4;

(2) when A^3 is $C(R^5)$, R^4 and R^5 may together comprise a heterocyclic ring; and

(3) when A^1 is $C(R^7)$, R^7 and R^3 may together comprise a heterocyclic ring including A^1 and the carbon atom to which R^3 is bonded;

(C) and provided that one of R^1, R^3, or R^6 is a covalent bond t L^1;

(II) B has a structure according to Formula (II):



(II)

wherein

(A) R^{10} is hydrogen, halogen, alkyl, alkenyl, heteroalkyl, a carbocyclic ring, a heterocyclic ring, R^8-O-, R^8CH=N-, $(R^8)(R^9)N$-, $R^{17}C(=CH-R^{20})-C(=O)NH$-, $R^{17}-C(=NO-R^{19})-C(=O)NH$, or $R^{18}-(CH_2)_m-C(=O)NH$- (preferably alkyl); where

(1) m is an integer from 0 to 9 (preferably from 0 to 3);

(2) R^{17} is hydrogen, alkyl, alkenyl, heteroalkyl, heteroalkenyl, a carbocyclic ring, or a heterocyclic ring (preferably alkyl, a carbocyclic ring, or a heterocyclic ring);

(3) R^{18} is R^{17}, $-Y^1$, or $-CH(Y^2)(R^{17})$;

(4) R^{19} is R^{17}, arylalkyl, heteroarylalkyl, $-C(R^{22})-(R^{23})COOH$, $-C(=O)O-R^{17}$, or $-C(=O)NH-R^{17}$, where R^{22} and R^{23} are, independently, R^{17} or together comprise a carbocyclic ring or a heterocyclic ring including the carbon atom to which R^{22} and R^{23} are bonded (preferably R^{17} $-C(R^{22})$ (R^{23})-COOH) or;

(5) R^{20} is R^{19}, halogen, $-Y^1$, or $-CH(Y^2)(R^{17})$ (preferably R^{19}or halogen);

(6) Y^1 is $-C(=O)OR^{21}$, $-C(=O)R^{21}$, $-N(R^{24})R^{21}$, $-S(O)_p R^{29}$, or $-OR^{29}$; and Y^2 is Y^1 or -OH, -SH, or $-SO_3H$;

(a) p is an integer from 0 to 2 (preferably 0);

(b) R^{24} is hydrogen; alkyl; alkenyl; heteroalkyl; heteroalkenyl; a carbo-cyclic ring; a heterocyclic ring; $-SO_3H$; $-C(=O)R^{25}$; or, when R^{18} is $-CH(N(R^{24})R^{21})(R^{17})$, R^{24} may comprise a moiety bonded to R^{21} to form a heterocyclic ring; and

(c) R^{25} is R^{17}, $-NH(R^{17})$, $-N(R^{17})(R^{26})$, $-O(R^{26})$, or $-S(R^{26})$; where R^{26} is alkyl, alkenyl, a carbocyclic ring, a heterocyclic ring, or (preferably) when R^{25} is $-N(R^{17})(R^{26})$, R^{26} may be a moiety bonded to R^{17} to form a heterocyclic ring; and

(7) R^{21} is R^{29} or hydrogen; where R^{29} is alkyl; alkenyl; arylalkyl; heteroalkyl; hetero-alkenyl; heteroarylalkyl; a carbocyclic ring; a heterocyclic ring; or, when Y is $-N(R^{24})R^{21}$ and R^{21} is R^{29}, R^{21} and R^{24} may together comprise a heterocyclic ring including the nitrogen atom to which R^{24} is bonded (preferably hydrogen, alkyl, a carbocyclic ring, or a heterocyclic

ring);

(B) R^{11} is hydrogen, halogen, alkoxy, or $R^{27}C(=O)NH$- (preferably hydrogen or alkoxy), where R^{27} is hydrogen or alkyl (preferably hydrogen);

(C) bond "a" is a single bond or is nil; and bond "b" is a single bond, a double bond, or is nil; except bond "a" and bond "b" are not both nil;

(D) R^{12} is $-C(R^8)-$, or $-CH_2-R^{28}-$ (preferably $-C(R^8)-$); where R^{28} is $-C(R^8)$, -O-, or -N-, and R^{28} is directly bonded to N" in Formula (II) to form a 5-membered ring;
except, if bond "a" is nil, then R^{12} is

(1) (preferably) $-C(R^8)(X^1)-$, where

(a) X^1 is $-R^{21}$; $-OR^{30}$; $-S(O)_rR^{30}$, where r is an integer from 0 to 2 (preferably 0); $-OC(=O)R^{30}$; or $-N(R^{30})R^{31}$; and

(b) R^{30} and R^{31} are, independently, alkyl, alkenyl, a carbocyclic ring or a heterocyclic ring; or R^{30} and R^{31} together comprise a heterocyclic ring including the nitrogen atom to which R^{30} and R^{31} are bonded; or

(2) $-CH_2-R^{32}-$; where R^{32} is $-C(R^8)(R^{21})$, -O-, or $-NR^8$, and R^{32} is directly bonded to N" in Formula (II) to form a 5-membered ring;

(E) (1) if bond "b" is a single bond, R^{13} is (preferably) $-CH(R^{33})-$; or, $-C(O)NHSO_2-$, if b nd "a" is nil; or $-C^*(R^{33})-$ if R^{14} contains a R^{36} m iety; where R^{33} is hydrogen or (preferably) $-COOR^{46}$, where R^{46} is hydrogen, alkyl, or alkenyl, and C is linked to R^{36} to form a 3-membered ring;

(2) if bond "b" is a double bond, R^{13} is $-C(R^{33})=$; or

(3) if bond "b" is nil, R^{13} is hydrogen, $-SO_3H$, $-PO(OR^{34})OH$, $-C(O)NHSO_2N(R^{34})(R^{35})$, $-OSO_3H$, $-CH(R^{35})COOH$, or $-OCH(R^{34})-COOH$ (preferably $-SO_3H$ or $-C(O)NH-SO_2N(R^{34})(R^{35})$); where R^{34} is hydrogen, alkyl, alkenyl, a carbocyclic ring, or a heterocyclic ring; and R^{35} is hydrogen, alkyl, alkenyl, or $-NHR^8$; or (preferably), if R^{13} is $-C(O)NH-SO_2N(R^{34})(R^{35})$, R^{34} and R^{35} may

together comprise a heterocyclic ring including the nitrogen to which R^{34} and R^{35} are bonded; and

(F) (1) if bond "a" or bond "b" is nil, then R^{14} is covalent bond;

(2) if bond "a" and "b" are single bonds, R^{14} is -W-C'''=C(R^8)-R^{37}-, or -W-C'''(R^{36})- R^{37}-; or

(3) (preferably) if bond "a" is a single bond and bond "b" is a double bond, R^{14} is -C(R^8)(R^{38})-W-C'''-R^{37}-; (preferably) -W-C(R^8)-(R^{38})-C'''-R^{37}-; or -W-C'''-R^{37}-;

(4) where

(a) W is O; $S(O)_s$, where s is an integer from 0 to 2 (preferably 0); or C(R^{38}), where R^{38} is hydrogen, alkyl or alkoxy;

(b) R^{36} is hydrogen; alkyl; alkenyl; -COOH; or, if R^{13} is -C*(R^{33}), R^{36} may be linked to C* to form a 3-membered carbocyclic ring;

(c) R^{37} is covalent bond, alkyl, alkenyl, a carbocyclic ring, or a heterocyclic ring; and

(d) C''' is directly bonded to R^{13} to form a 5- r 6-membered ring; and

(III) (A) L is -C(=Z)-; -$S(O)_v$-; -N(R^{44})-; -N^+(R^{44})(R^{45})-; -N(R^{44})-N(R^{44})-; -O-; =N-; or a covalent bond (preferably -C(=Z)-; -N(R^{44})); and L is bonded to L^3 and L^4; where

(1) Z is O, S, or $^+N(H)_2$ (preferably O or S);

(2) v is 0, 1 or 2;

(3) R^{44} is, independently, hydrogen, substituted r unsubstituted lower alkyl, aryl, acyl, hydroxy, alkoxy, aryloxy, or acyloxy (preferably hydrogen r substituted or unsubstituted lower alkyl); and

(4) R^{45} is hydrogen, (preferably) unsubstituted or substituted lower alkyl, or substituted r unsubstituted aryl;

(B) L^1 is L^3 or $R^{15}L^3$; where

(1) when L is -C(=Z)-, L^3 is a covalent bond, oxygen, sulfur, or (preferably) nitrogen; and when L is other than -C(=Z)-, L^3 is a covalent bond;

(2) R^{15} is alkyl, alkenyl, heteroalkyl, a heterocyclic ring,

a carbocyclic ring, or R^{15} together with L^3 is a heteroalkyl or a heterocyclic ring; and

(3) L^1 is bonded to Q at the point of attachment of R^1, R^3 or R^6, whichever is a covalent bond;

(C) L^2 is L^4, $-X^2_t-R^{39}-L^4$, or $-X^3_t-R^{39}-L^4$; where

(1) (preferably) when L is -C(=Z)-, L^4 is a covalent bond, oxygen, sulfur, or nitrogen (preferably oxygen or sulfur); and when L is other than -C(=Z)-, L^4 is a covalent bond;

(2) X^2 is oxygen, or $S(O)_v$, where v is 0, 1, or 2;

(3) X^3 is nitrogen; $N(R^{40})$; $N^+(R^{41})(R^{42})$; or R^{43}-$N(R^{41})$; and is linked to R^{14} by a single or double bond; or, if R^{14} is covalent bond, X^3 is linked to B by a single or double bond (preferably nitrogen; $N(R^{40})$; $N^+(R^{41})(R^{42})$); where

(a) R^{40} is R^8; $-OR^8$; or $-C(=O)R^8$ (preferably R^8);

(b) R^{41} and R^{42} are, independently, hydrogen; alkyl; alkenyl; carbocyclic rings; heterocyclic rings; or, if R^6 is $R^{16}X$, then R^{41} and R^{42} together with Q" may comprise a heterocyclic ring as R^{16};

(c) R^{43} is $N(R^{41})$, oxygen or sulfur;

(4) t is 0 or 1;

(5) R^{39} is alkyl, alkenyl, heteroalkyl, heteroalkenyl, a carbocyclic ring, or a heterocyclic ring; and

(6) (a) if bond "a" or bond "b" is nil, then L^2 is bonded directly to R^{12} or R^{13}; or

(b) if bond "a" and bond "b" are not nil, then L^2 is bonded to R^{14};

(D) provided that if L^1, L^2 and R^{37} is each a covalent bond, then L is not a covalent;

or a protected form, salt, pharmaceutically-acceptable salt, biohydrolyzable ester, or solvate thereof. Preferred antimicrobial QLAs made by the processes of this invention include those where R^3 is a covalent bond to L^1, and those where R^6 is a covalent bond to L^1.

Where th QLAs synthesized using the present methods are used as intermediates, they may contain various functi nal groups (e.g., alc hols,

amines, carboxylic acids, etc.) that may be present in a protected f rm, utilizing protecting groups (e.g., esters, carbonates, ethers, silyl ethers, amides, carbamates, etc.) introduced by methods well known in the art. The art is also replete with methodology to remove these protecting groups. Where the compounds synthesized are used as antimicrobials, they may be in acid form, or as a pharmaceutically-acceptable salt, biohydrolyzable ester or solvate thereof.

Intermediates

The novel intermediates of the present invention have a structure according the formula (M - L^1) - L - (L^2 - B), where M has a structure according to Formula (IV) and B has a structure according to Formula (II). The Formula (III) compound are prepared by coupling a compound of Formula (III) with a lactam compound of Formula (II). Preferred substituents for the "M" component (Formula (IV)) are the same as those listed for the Formula (I) component (quinolone) of the QLAs. Similarly, preferred substituents for L^1, L, L^2 and B are the same as those listed for the QLAs. These intermediates may be coupled to the lactam moiety under reaction conditions that are less harsh than those described in the literature, and may therefore allow for improved QLA yields and purities.

Examples of the intermediate compounds of the present invention are described hereinbelow.

Definitions and Usage of Terms:

The following is a list of definitions for terms used herein.

"Acyl" or "carbonyl" is a radical formed by removal of the hydroxy from an carboxylic acid (i.e., R-C(=O)-). Preferred alkylacyl groups include (for example) acetyl, formyl, and propionyl.

"Acyloxy" is an oxygen radical having an acyl substituent (i.e., -O-acyl); for example,-O-C(=O)-alkyl.

"Acylamino" is an amino radical having an acyl substituent (i.e., -N-acyl); for example, -NH-C(=O)-alkyl.

"Alkyl" is an unsubstituted or substituted saturated hydrocarbon chain radical having from 1 to 8 carbon atoms, preferably from 1 to 4 carbon atoms. Preferred alkyl groups include (for example) methyl, ethyl, propyl, isopropyl, and butyl.

"Alkenyl" is an unsubstituted or substituted hydrocarbon chain radical having from 2 to 8 carbon atoms, preferably from 2 to 4 carbon atoms, and having at least one olefinic double bond.

"Alk xy" is an oxygen radical having a hydrocarb n chain substituent, where the hydrocarbon chain is an alkyl or alkenyl (i.e., -O-alkyl or -O-alkenyl). Preferred alkoxy groups include (for example) methoxy, ethoxy, propoxy and

allyloxy.

"Alkylamino" is an amino radical having one or two alkyl substituents (i.e., -N-alkyl).

"Aryl" is an aromatic carbocyclic ring radical. Preferred aryl groups include (for example) phenyl, tolyl, xylyl, cumenyl and naphthyl.

"Arylalkyl" is an alkyl radical substituted with an aryl group. Preferred arylalkyl groups include benzyl and phenylethyl.

"Arylamino" is an amine radical substituted with an aryl group (i.e., -NH-aryl).

"Aryloxy" is an oxygen radical having a aryl substituent (i.e., -O-aryl).

"Carbocyclic ring" is an unsubstituted or substituted, saturated, unsaturated or aromatic, hydrocarbon ring radical. Carbocyclic rings are monocyclic or are fused, bridged or spiro polycyclic ring systems. Monocyclic rings contain from 3 to 9 atoms, preferably 3 to 6 atoms. Polycyclic rings contain from 7 to 17 at ms, preferably from 7 to 13 atoms.

"Cycloalkyl" is a saturated carbocyclic ring radical. Preferred cycloalkyl groups include (for example) cyclopropyl, cyclobutyl and cyclohexyl.

"Halo", "halogen", or "halide" is a chloro, bromo, fluoro or iodo atom radical. Chloro and fluoro are preferred halides.

"Heteroatom" is a nitrogen, sulfur or oxygen atom. Groups containing one or more heteroatoms may contain different heteroatoms.

"Heteroalkyl" is an unsubstituted or substituted saturated chain radical having from 3 to 8 members comprising carbon atoms and one or two heteroat ms.

"Heteroalkenyl" is an unsubstituted or substituted chain radical having from 2 to 8 carbon atoms, preferably from 2 to 6 carbon atoms, having at least ne olefinic double bond, and having one or two heteroatoms.

"Heterocyclic ring" is an unsubstituted or substituted, saturated, unsaturated or aromatic ring radical comprised of carbon atoms and one or more heteroatoms in the ring. Heterocyclic rings are monocyclic or are fused, bridged or spiro polycyclic ring systems. Monocyclic rings contain from 3 to 9 atoms, preferably 4 to 8 atoms, more preferably from 5 to 8 atoms, most preferably from 4 to 6 at ms. Polycyclic rings contain from 7 to 17 atoms, preferably from 7 to 13 atoms.

"Heterocycloalkyl" is a saturated heterocyclic ring radical. Preferred heterocycloalkyl groups include (for example) piperazine, pyrrolidine, piperadine, and morpholine.

"Heteroaryl" is an aromatic heterocyclic ring radical. Preferred heter aryl groups include (for example) thienyl, furyl, pyrrolyl, pyridinyl, pyrazinyl, thiazolyl, quinolinyl, pyrimidinyl and tetrazolyl.

"Heteroarylalkyl" is an alkyl radical substituted with an heteroaryl group. Also, as referred to herein, a "lower" hydrocarbon moiety (e.g., "lower" alkyl) is a hydrocarbon chain comprised of from 1 to 6, preferably from 1 to 4, carbon atoms.

"Organosilicon compounds", as referred to herein, are those silicon-containing compounds that are commonly utilized in silylation reactions, that is, reactions which substitute a hydrogen atom bound to a heteroatom (e.g., -OH, =NH, -SH, etc.) with a silyl group, usually a trialkylsilyl group, including reactions of a tautomer of a heteroatom system to form a silyl derivative (e.g., silyl enol ethers), forming a silicon - heteroatom bond. Many such reagents are well known in the art, as described in the following articles, all incorporated by reference herein: E. Plueddemann, "Silylating Agents", in: Kirk-Othmer, 3d ed., Vol. 20, "Encyclopedia of Chemical Technology" (1982); I. Fleming, "Organic Silicon Chemistry", in: Vol. 3, "Comprehensive Organic Chemistry" (D. Jones, editor, 1979); B. Cooper, "Silylation in Organic Synthesis", Proc. Biochem. 9 (1980); W. Weber, "Silicon Reagents for Organic Synthesis (1983); B. Cooper, "Silylation as a Protective Method in Organic Synthesis, Chem. Ind. 794 (1978); J. Rasmussen, "O-Silylated Enolates - Versatile Intermediates for Organic Synthesis" 91 Synthesis (1977). Such organosilicon compounds include chlorotrimethylsilane, N,O-bis(trimethylsilyl)acetamide, N,O-bis(trimethylsilyl)-trifluoroacetamide, bis(trimethylsilyl)urea, hexamethyldisilazane, N-methyl-N-trimethylsilyl-trifluoroacetamide, 1-trimethylsilylimidazole, trimethylsilyl trifluoromethanesulfonate, tert-butyldimethylchlorosilane, 1-(tert-butyldimethylsilyl)-imidazole, N-tert-butyldimethyl-N-methyltrifluoroacetamide, tert-butyldimethylsilyl trifluoromethanesulfonate, tert-butyldiphenylchlorosilane, tert-butyl-methoxy-phenylbromosilane, dimethylphenylchlorosilane, triethylchlorosilane, triethylsilyl trifluoromethanesulfonate, and triphenylchlorosilane.

A "protected form", as referred to herein, is a derivative of the described compound wherein certain functional groups contained in the structures (such as carboxyl, hydroxyl, and amino groups) are blocked in order to prevent undesired competing side reactions and, occasionally, to improve the solubility of the compound. Suitable protecting groups for carboxyl substituents include, for example, esters. Protecting groups for hydroxyl substituents include, for example, ethers, esters, and carbonates; and protecting groups for amino substituents include, for example, carbamates and amides. If various protecting groups are employed, then appropriate methods for introducing and removing the protecting groups, that will not decompose the quinolone or related heterocyclic compound, may be required to efficiently obtain antibacterially active products or intermediates thereof.

Appr priate protecting groups for these processes are well known in the art.

For hydroxyl groups, suitable derivatives include, for example, alkyl ethers [such as allyl, tert-butyl, and 2-(trimethylsilyl)ethoxymethyl], silyl ethers (such as trimethylsilyl, tert-butyldimethylsilyl, tert-butyldiphenylsilyl), esters (such as acetate and trifluoroacetate) and carbonates (such as allyl and vinyl). For amines, suitable carbamates include, for example, tert-butyl and 2-trimethylsilyl, and suitable amides include, for example, trifluoroacetamide. For carboxylic acids, suitable esters include, for example, allyl, p-methoxybenzyl, p-nitrobenzyl, diphenylmethyl, 2,2,2-trichloroethyl, 2-trimethylsilylethyl, 2-methylthioethyl, trimethylsilyl, t-butyldiphenylsilyl, t-butyl, and tributylstannyl esters. Such protecting groups and methods for their introduction and removal are described in T. W. Greene et al., Protective Groups in Organic Synthesis, 2d edition, J. Wiley and Sons (1991), incorporated by reference herein.

A "biohydrolyzable ester" is an ester of a QLA that does not essentially interfere with the antimicrobial activity of the compounds, or that are readily metabolized by a human or lower animal subject to yield an antimicrobially-active quinolonyl lactam. Such esters include those that do not interfere with the biological activity of quinolone antimicrobials or beta-lactam antimicrobials (cephems, for example). Many such esters are known in the art, as described in World Patent Publication 87/05297, Johnston et al., published September 11, 1987, (incorporated by reference herein). Such esters include lower alkyl esters, l wer acyloxy-alkyl esters (such as acetoxymethyl, acetoxyethyl, aminocarbonyloxymethyl, pivaloyloxymethyl and pivaloyloxyethyl esters), lactonyl esters (such as phthalidyl and thiophthalidyl esters), lower alkoxyacyloxyalkyl esters (such as methoxycarbonyloxymethyl, ethoxycarbonyloxyethyl and isoprop xy-carbonyloxyethyl esters), alkoxyalkyl esters, choline esters and alkyl acylamino alkyl esters (such as acetamidomethyl esters).

As defined above and as used herein, substituent groups may themselves be substituted. Such substitution may be with one or more substituents. Such substituents include (for example) those listed in C. Hansch and A. Leo, Substituent Constants for Correlation Analysis in Chemistry and Biology (1979), incorporated by reference herein. Preferred substituents include (for example) alkyl, alkenyl, alkoxy, hydroxy, oxo, nitro, amino, aminoalkyl (e.g., aminomethyl, etc.), cyano, halo, carboxy, alkoxyaceyl (e.g., carboethoxy, etc.), thiol, aryl, cycloalkyl, heteroaryl, heterocycloalkyl (e.g., piperidinyl, morpholinyl, pyrrolidinyl, etc.), imino, thioxo, hydroxyalkyl, aryloxy, arylalkyl, and combinations thereof.

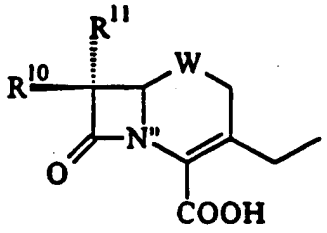
Also, as used in defining the structure of the compounds of this inventi n, a particular radical may be defined for use as a substituent in multiple l cati ns. F r example, the R^8 substituent is defined as a potential substituent of R^7, but is also

incorporated into the definition of other substituents (such as R^1, R^6, and R^{10}). As used herein, such a radical is independently selected each time it is used (e.g., R^8 need not be alkyl in all occurrences in defining a given compound of this invention).

Lactam-containing moiety:

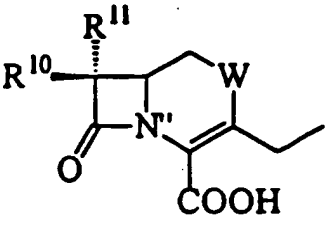
Groups R^{12}, R^{13}, and R^{14}, together with bonds "a" and "b" of formula (II), form any of a variety of lactam-containing moieties known in the art to have antimicrobial activity. Such moieties wherein either bond "a" or bond "b" are nil (i.e., do not exist) are monocyclic; if both bonds exist, the structures are bicyclic. Preferably, bond "a" is a single bond and bond "b" is a double bond.

Preferred lactam moieties include the cephems, oxacephems and carbacephems of the representative formula:



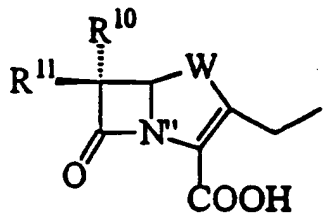
wherein, referring to formula (II), bond "a" is a single bond; bond "b" is a double bond; R^{12} is $-C(R^8)-$, where R^8 is hydrogen; R^{13} is $-C(R^{33})=$, where R^{33} is COOH; and R^{14} is $-W-C(R^8)(R^{38})-C'''-R^{37}$, where R^8 and R^{38} are hydrogen, R^{37} is methylene, and W is S (for cephems), O (for oxacephems) or $C(R^{38})$ (for carbacephems).

Other preferred lactam moieties include the isocephems and iso-oxacephems of the representative formula:



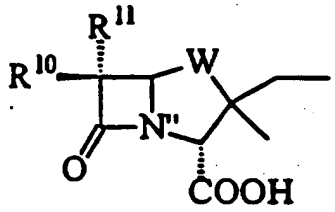
wherein, referring to formula II, bond "a" is a single bond; bond "b" is a double bond; R^{12} is $-C(R^8)$ where R^8 is hydrogen; R^{13} is $-C(R^{33})=$, where R^{33} is COOH; and R^{14} is $-C(R^8)(R^{38})-W-C'''-R^{37}$ where R^8 and R^{38} are each hydrogen, R^{37} is methylene, and W is S (for isocephems) or O (for iso-oxacephems).

Other preferred lactam-containing moieties include the penems, carbapenems and clavems, of the representative formula:



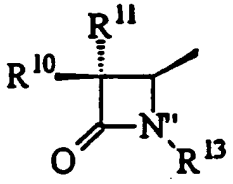
wherein, referring to formula (II), bond "a" is a single bond; bond "b" is a double bond; R^{12} is $-C(R^8)$, where R^8 is hydrogen; R^{13} is $-C(R^{33})=$, where R^{33} is COOH; and R^{14} is $-W-C'''-R^{37}$, where R^{37} is methylene, and W is S (for penems), $C(R^{38})$ (for carbapenems), or O (for clavems). Such lactam moieties are described in the following articles, all incorporated by reference herein: R. Wise, "In Vitro and Pharmacokinetic Properties of the Carbapenems", 30 Antimicrobial Agents and Chemotherapy 343 (1986); and S. McCombie et al., "Synthesis and In Vitro Activity of the Penem Antibiotics", 8 Medicinal Research Reviews 393 (1988).

Other preferred lactam-containing moieties of this invention include the penicillins of the representative formula:



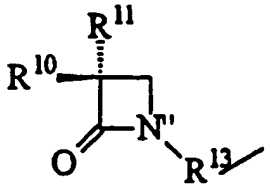
wherein, referring to formula II, bond "a" is a single bond, bond "b" is a single bond; R^{12} is $-C(R^8)-$, where R^8 is hydrogen; R^{13} is $-CH(R^{33})-$ where R^{33} is COOH; and R^{14} is $-W-C'''(R^{36})-R^{37}-$ where R^{36} is methyl, R^{37} is methylene, and W is S.

Other preferred lactam-containing moieties include the monocyclic beta-lactams, of the representative formula:



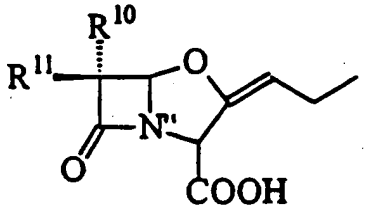
wherein, referring to formula (II), bond "a" is a single bond; bond "b" is nil; R^{12} is $-C(R^8)-$, where R^8 is hydrogen; R^{14} is covalent bond; and R^{13} is $-SO_3H$ (for a monobactam), $-PO(OR^{34})OH$ (for a monophospham); $-C(O)NHSO_2N(R^{34})(R^{35})$ (for a monocarbam), $-OSO_3H$ (for a monosulfactam), $-CH(R^{35})COOH$ (for nocardicins), or $-OCH(R^{34})COOH$. Such lactam moieties are described in C. Cimarusti et al., "Monocyclic 8-lactam Antibiotics", 4 Medicinal Research Reviews 1 (1984), incorporated by reference herein.

Other preferred lactam moieties include the monocyclic beta-lactams of the representative formula:



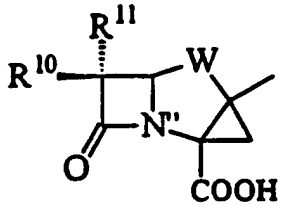
wherein referring to formula II, bond "a" is nil, bond "b" is a single bond; R^{12} is $-C(R^8)(R^{29})-$ where both R^8 and R^{29} are hydrogen; and R^{14} is covalent bond.

Other preferred lactam moieties include the clavams of the representative formula:



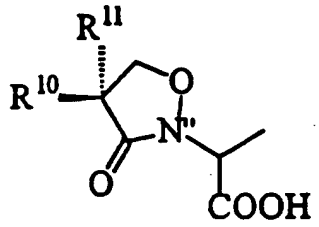
wherein, referring to formula (II), bond "a" is a single bond; bond "b" is a single bond; R^{12} is $-C(R^8)-$, where R^8 is hydrogen; R^{13} is $-CH(R^{33})-$, where R^{33} is COOH; and R^{14} is $W\text{-}C'''=C\text{-}(R^8)\text{-}R^{37}$, where R^8 is hydrogen and R^{37} is methylene, and W is O.

Other preferred lactam moieties include the 2,3-methyleno-penams and carbapenams of the representative formula:



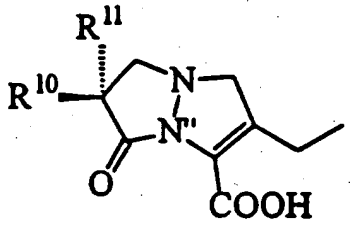
wherein, referring to formula (II), bond "a" is a single bond; bond "b" is a single bond; R^{12} is $-C(R^8)-$, where R^8 is hydrogen; R^{13} is $-C^*(R^{33})$, where R^{33} is COOH; and R^{14} is $W\text{-}C'''(R^{36})\text{-}R^{37}$, where R^{37} is covalent bond, R^{36} is linked to C^* to form a 3-membered carbocyclic ring, and W is $C(R^{38})$ or sulfur.

Lactam moieties of this invention also include the lactivicin analogs of the representative formula:



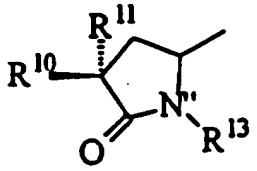
wherein, referring to formula (II), bond "a" is nil; bond "b" is a single bond; R^{12} is $-CH_2-R^{32}$, where R^{32} is O; R^{13} is $-CH(R^{33})-$, where R^{33} is COOH; and R^{14} is covalent bond.

Other lactam moieties include the pyrazolidinones of the representative formula:



wherein, referring to formula (I), bond "a" is a single bond; bond "b" is a double bond; R^{12} is $-CH_2-R^{28}-$, where R^{28} is -N-; R^{13} is $-C(R^{33})-$, where R^{33} is COOH; and R^{14} is $W-C'''-R^{37}-$, where R^{37} is methylene, and W is $C(R^{38})$.

Other lactam moieties include the gamma-lactams of the representative formula:



wherein, referring to formula (II), bond "a" is a single bond; bond "b" is nil; R^{12} is $-CH_2-R^{28}-$, where R^{28} is $-C(R^8)$ and R^8 is hydrogen; R^{13} is $-SO_3H$, $-PO(OR^{34})OH$, $-C(O)NHSO_2N(R^{34})(R^{35})$, $-OSO_3H$, $-CH(R^{35})COOH$, or $-OCH(R^{34})COOH$; and R^{14} is covalent bond.

Preferred lactam-containing moieties include cephems, isocephems, isoxacephems, oxacephems, carbacephems, penicillins, penems, carbapenems, and monocyclic beta-lactams. Particularly preferred lactam-containing moieties for compounds made by this invention are penems, carbapenems, cephems, and carbacephems.

R^{10}, in formula (II), is any radical that may be substituted at the active stereoisomeric position of the carbon adjacent to the lactam carbonyl of an antimicrobially-active lactam. (As used herein, the term "antimicr bially-active

lactam" refers to a lactam-containing compound, without a quinolonyl substituent moiety, which has antimicrobial activity.) This "active" position is beta (i.e., 7-beta) for oxacephems and carbacephems (for example). The active position is alpha for penems, carbapenems, clavems and clavams.

Appropriate R^{10} groups will be apparent to one of ordinary skill in the art. Many such R^{10} groups are known in the art, as described in the following documents (all of which are incorporated by reference herein): Cephalosporins and Penicillins: Chemistry and Biology (E. Flynn, editor, 1972); Chemistry and Biology of β-Lactam Antibiotics (R. Morin et al., editors, 1987); "The Cephalosporin Antibiotics: Seminar-in-Print", 34 Drugs (Supp. 2) 1 (J. Williams, editor, 1987); New Beta-Lactam Antibiotics: A Review from Chemistry of Clinical Efficacy of the New Cephalosporins (H. Neu, editor, 1982); M. Sassiver et al., in Structure Activity Relationships among the Semi-synthetic Antibiotics (D. Perlman, editor, 1977); W. Durckheimer et al., "Recent Developments in the Field of Beta-Lactam Antibiotics", 24 Angew. Chem. Int. Ed. Engl. 180 (1985); G. Rolinson, "Beta-Lactam Antibiotics", 17 J. Antimicrobial Chemotherapy 5 (1986); European Patent Publication 187,456, Jung, published July 16, 1986; and World Patent Publication 87/05297, Johnston et al., published September 11, 1987.

For penems, carbapenems, clavems and clavams, R^{10} is preferably lower alkyl, or hydroxy-substituted lower alkyl. Particularly preferred R^{10} groups include hydrogen, hydroxymethyl, ethyl, [1(R)-hydroxyethyl], [1(R)-[(hydroxysulfonyl)oxyethyl]], and [1-methyl-1-hydroxyethyl].

Except for penems, carbapenems, clavems and clavams, preferred R^{10} groups are amides, such as: acetylamino, preferably substituted with aryl, heteroaryl, aryloxy, heteroarylthio and lower alkylthio substituents; arylglycylamino, preferably N-substituted with heteroarylcarbonyl and cycloheteroalkylcarbonyl substituents; arylcarbonylamino; heteroarylcarbonylamino; and lower alkoxyiminoacetylamino, preferably substituted with aryl and heteroaryl substituents. Particularly preferred R^{10} groups include amides of the general formula R^{18}-$(CH_2)_m$-C(=O)NH- and R^{18} is R^{17}. Examples of such preferred R^{10} groups include:

[(2-amino-5-halo-4-thiazolyl)acetyl]amino;
[(4-aminopyridin-2-yl)acetyl]amino;
[[(3,5-dichloro-4-oxo-1(4H)-pyridinyl)acetyl]amino];
[[[2-(aminomethyl)phenyl]acetyl]amino];
[(1H-tetrazol-1-ylacetyl)amino];
[(cyanoacetyl)amino];
[(2-thienylacetyl)amino];

[[(2-amino-4-thiazoyl)acetyl]amino]; and

sydnone, 3-[-2-amino]-2-oxoethyl.

When R^{10} is R^{18}-$(CH_2)_m$-C(C=O)NH-, and R^{18} is $-Y^1$, preferred R^{10} groups include the following:

[sulfamoylphenylacetyl]amino;

[[(4-pyridinylthio)acetyl]amino];

[[[(cyanomethyl)thio]acetyl]amino];

(S)-[[[(2-amino-2-carboxyethyl)thio]acetyl]amino];

[[[(trifluoromethyl)thio]acetyl]amino]; and

(E)-[[[(2-aminocarbonyl-2-fluoroethenyl)thio]acetyl]amino].

When R^{10} is R^{18}-$(CH_2)_m$-C(=O)NH-, and R^{18} is $-CH(Y^2)(R^{17})$, preferred R^{10} groups include the following:

[carboxyphenylacetyl]amino;

[(phenoxycarbonyl)phenylacetyl]amino;

[4-methyl-2,3-dioxo-1-piperazinecarbonyl-D-phenylglycyl]amino;

[[[3-(2-furylmethyleneamino)-2-oxo-1-imidazolidinyl]carbonyl]amino]phenyl]-acetyl]amino;

(R)-[(aminophenylacetyl)amino];

(R)-[[amino(4-hydroxyphenyl)acetyl]amino];

(R)-[(amino-1,4-cyclohexadien-1-ylacetyl)amino];

[(hydroxyphenylacetyl)amino];

(R)-[[[[(4-ethyl-2,3-dioxo-1-piperazinyl)carbonyl]amino](4-hydroxy-phenyl)acetyl]amino];

(R)-[[[[(5-carboxy-1H-imidazol-4-yl)carbonyl]amino]phenylacetyl]amin];

(R)-[[[[(4-hydroxy-6-methyl-3-pyridinyl)carbonyl]amino](4-hydroxyphenyl)acetyl]amino];

(R)-[(phenylsulfoacetyl)amino];

(2R,3S)-[[2-[[(4-ethyl-2,3-dioxo-1-piperazinyl)carbonyl]amino]-3-hydr xy-1-oxobutyl]amino];

[[carboxy(4-hydroxyphenyl)acetyl]amino];

(R)-[[amino[3-[(ethylsulfonyl)amino]phenyl]acetyl]amino];

(R)-[[amino(benzo[b]thien-3-yl)acetyl]amino];

(R)-[[amino(2-naphthyl)acetyl]amino];

(R)-[[amino(2-amino-4-thiazolyl)acetyl]amino];

[[[[(6,7-dihydroxy-4-oxo-4H-1-benzopyran-3-yl)carbonyl]amino](4-hydroxyphenyl)acetyl]amino];

(R,R)-[[2-[4-[2-amino-2-carb xyethyloxycarbonyl]aminophenyl]-2-hydroxyacetyl]amino]; and

(S)-[[(5-hydroxy-4-oxo-1(4H)-pyridin-2-yl)carbonylamino(2-amino-4-thiazolyl)acetyl]amino].

Another preferred R^{10} group is R^{17}-C(=CHR^{20})-C(=O)NH-. Another class of preferred R^{10} groups (for lactam-containing moieties other than penems, carbapenems, clavems and clavams) include those of the formula:

$$R^{17}\text{-C(=NO-}R^{19}\text{)-C(=O)NH-}.$$

Examples of this preferred class of R^{10} groups include:

2-phenyl-2-hydroxyiminoacetyl;

2-thienyl-2-methoxyiminoacetyl; and

2-[4-(gamma-D-glutamyloxy)phenyl]-2-hydroxyiminoacetyl.

(Z)[[(2-amino-4-thiazolyl)(methoxyimino)acetyl]amino];

[[(2-furanyl(methoxyimino)acetyl]amino];

(Z)-[[(2-amino-4-thiazolyl)[(1-carboxy-1-methyl)ethoxyimino]acetyl]amino];

(Z)-[[(2-amino-4-thiazolyl)(1-carboxymethoxyimino)acetyl]amino];

[[(2-amino-4-thiazolyl)[(1H-imidazol-4-ylmethoxy)imino]acetyl]amino];

(Z)-[[(2-amino-4-thiazolyl-3-oxide)(methoxyimino)acetyl]amino]; and

(S,Z)-[[(2-amino-4-thiazolyl)[carboxy(3,4-dihydroxyphenyl)-methoxyimino]acetyl]amino].

Suitable R^{11} groups are among those well-known in the art, including those defined in the following documents (all incorporated by reference herein). W. Durckheimer et al., "Recent Developments in the Field of Beta-Lactam Antibiotics", 24 Angew. Chem. Int. Ed. Engl. 180 (1985); G. Rolinson, "Beta-Lactam Antibiotics", 17 J. Antimicrobial Chemotherapy 5 (1986); and European Patent Publication 187,456, Jung, published July 16, 1986. Preferred R^{11} groups include hydrogen, methoxy, ethoxy, propoxy, thiomethyl, halogen, cyano, formyl and formylamino. Particularly preferred R^{11} groups include hydrogen, methoxy, halogen, and formylamino.

Quinolone Moieties:

Groups A^1, A^2, A^3, R^1, R^3, and R^4 of Formula I form a moiety (herein, "quinolone moiety") present in any of a variety of quinolone, naphthyridine or related heterocyclic compounds known in the art to have antimicrobial activity. Such heterocyclic moieties are well known in the art, as described in the following articles, all incorporated by reference herein: J. Wolfson et al., "The Fluoroquinolones: Structures, Mechanisms of Action and Resistance, and Spectra of Activity In Vitro", 28 Antimicrobial Agents and Chemotherapy 581 (1985); and T. Rosen et al., 31 J. Med Chem. 1586 (1988); T. Rosen et al., 31 J. Med. Chem. 1598 (1988); G. Klopman et al., 31 Antimicrob. Agents Chemother. 1831 (1987);

31:1831-1840; J. P. Sanchez et al., 31 J. Med. Chem. 983 (1988); J. M. D magala et al., 31 J. Med. Chem. 991 (1988); M. P. Wentland et al., in 20 Ann. Rep. Med. Chem. 145 (D. M. Baily, editor, 1986); J. B. Cornett et al., in 21 Ann. Rep. Med. Chem. 139 (D. M. Bailey, editor, 1986); P. B. Fernandes et al., in 22 Ann. Rep. Med. Chem. 117 (D. M. Bailey, editor, 1987); R. Albrecht, 21 Prog. Drug Research 9 (1977); and P. B. Fernandes et al., in 23 Ann. Rep. Med. Chem. (R. C. Allen, editor, 1987).

Preferred quinolone moieties include those where A^1 is $C(R^2)$, A^2 is $C(R^2)$, and A^3 is $C(R^5)$ (i.e., quinolones); A^1 is nitrogen, A^2 is $C(R^2)$, and A^3 is $C(R^5)$ (i.e., naphthyridines); A^1 is $C(R^7)$, A^2 is $C(R^2)$, and A^3 is nitrogen (i.e., cinn line acid derivatives); and where A^1 is nitrogen, A^2 is nitrogen, and A^3 is $C(R^5)$ (i.e., pyridopyrimidine derivatives). More preferred quinolone moieties are those where A^1 is $C(R^7)$, A^2 is $C(R^2)$, and A^3 is $C(R^5)$ (i.e., quinolones); and where A^1 is nitrogen, A^2 is $C(R^2)$, and A^3 is $C(R^5)$ (i.e., naphthyridines). Particularly preferred quinolone moieties are where A^1 is $C(R^7)$, A^2 is $C(R^2)$; and A^3 is $C(R^5)$ (i.e., quinolones).

R^1 is preferably alkyl, aryl, cycloalkyl and alkylamino. More preferably, R^1 is ethyl, 2-fluoroethyl, 2-hydroxyethyl, t-butyl, 4-fluorophenyl, 2,4-difluorophenyl, methylamino and cyclopropyl. Cyclopropyl is a particularly preferred R^1 group.

Preferred quinolone moieties also include those where A^1 is $C(R^7)$ and R^1 and R^7 together comprise a 6-membered heterocyclic ring containing an oxygen r sulfur atom. These compounds are prepared by an additional reaction step subsequent to the cyclization step (2) described herein. Specifically, after the QLA (wherein "Q" has two fused rings) is formed using the processes of the present invention, the third fused ring (i.e., between N' and A^1) is formed by methods known in the art. (See, for example, Bouzard et al., "Utilisation du Fluorure de Tetrabutylammonium comme Agent de Cyclisation dans la Synthese D'Antibacteriens Derives D'Acide Pyridone-4-Carboxylique-3", 29 Tet. Lett. 1931-1934 (1988)).

R^2 is preferably hydrogen or halo. More preferably R^2 is chlorine r fluorine. Fluorine is a particularly preferred R^2 group.

Preferred R^3 groups include nitrogen-containing heterocyclic rings. Particularly preferred are nitrogen-containing heterocyclic rings having from 5 to 8 members. The heterocyclic ring may contain additional heteroatoms, such as oxyg n, sulfur, or nitrogen, preferably nitrogen. Such heterocyclic groups are described in U.S. Patent 4,599,334, Petersen et al., issued July 8, 1986; and U.S. Patent 4,670,444, Grohe et al., issued June 2, 1987 (both incorporated by reference herein). Preferred R^3 groups include unsubstituted or substituted pyridine,

piperidine, morpholine, diazabicyclo-[3.1.1]heptane, diazabicyclo[2.2.1]heptane, diazabicyclo[3.2.1]octane, diazabicyclo-[2.2.2] octane, thiazolidine, imidazolidine, pyrrole and thiamorpholine, as well as the following particularly preferred R^3 groups include piperazine, 3-methylpiperazine, 3-aminopyrrolidine, 3-aminomethylpyrrolidine, 3-(1-aminoethyl)pyrrolidine, N,N-dimethylaminomethyl-pyrrolidine, N-methylaminomethylpyrrolidine, N-ethylaminomethylpyrrolidine, pyridine, N-methylpiperazine, and 3,5-dimethylpiperazine.

QLAs made by the processes of the present invention preferably have a quinolone moiety (Formula (I)) that is member of one of the following classes f compounds.

1. A^1 is -C(R^7)-; A^2 is -CF-; and A^3 is -CH-;
2. A^1 is -CH-, -CF-, -CCl-; A^2 is -CF-; A^3 is -CH-; R^4 is OH and pharmaceutically-acceptable salts; R^6 is H; and R^1 is cyclopropyl, ethyl, 2,4-difluorophenyl, 4-fluorophenyl, or t-butyl;
3. A^1 is -N-; A^2 is -CF-; and A^3 is -CH-;
4. A^1 is -N-; A^2 is -CF-; A^3 is -CH-; R^4 is OH and pharmaceutically-acceptable salts; R^6 is H; and R^1 is cyclopropyl, ethyl, 2,4-difluorophenyl, 4-fluorophenyl, or t-butyl; and
5. R^1, R^3, or R^6 is a lactam-containing moiety.

Linking Moieties:

A variety of linking moieties may be employed for attaching the quinolone and lactam moieties. Such linking moieties include, for example, carbamates, secondary amines, tertiary amines, quaternary amines (i.e., ammonium), heteroarylium, thioethers, ethers, dithiocarbamates, ureas, thioureas, imines, guanidiniums, carbonates, trithiocarbonates, reverse carbamates, xanthate, reverse dithiocarbamate. These and other useful linking moieties are described in European Patent Publication 366,189, White and Demuth, published May 2, 1990. Preferred linking moieties are carbamates, secondary amines, tertiary amines, quaternary amines, and dithiocarbamates. Particularly preferred are carbamates, secondary amines and tertiary amines.

The specific physical, chemical, and pharmacological properties of the quinolonyl lactams of this invention may depend upon the particular combination of the integral lactam-containing moiety, quinolone moiety and linking m iety comprising the compound. For example, selection of particular integral moieties may affect the relative susceptibility of the quinolonyl lactam to bacterial resistance

mechanisms (e.g., beta-lactamase activity).

Preferred lactam moieties, quinolone moieties, linking moieties, and QLAs are described in the following documents, all of which are incorporated by reference herein: European Patent Publication 366,189, White and Demuth, published May 2, 1990; European Patent Publication 335, 297, Albrecht et al., published Oct ber 4, 1989; and U.S. Patent Application Serial No. 07/511,483, Demuth and White, filed April 18, 1990.

Methods of Manufacture

The processes of this invention, when making a QLA, comprise the steps of:

(1) coupling a compound having a structure according to Formula (III) with a lactam compound of the Formula (II) to form an intermediate compound; and

(2) cyclizing the intermediate by reaction with an organosilicon compound to give Q-L-B.

The intermediate compounds (M-L^1-L-L^2-B) of the present invention are prepared by the coupling step (1).

The identity of the compound of Formula (III) and the lactam compound used in coupling Step (1) will be dictated, in part, by the linking group (i.e., -L^1-L-L^2-) of the desired intermediate or QLA end product. Using the present disclosure, those skilled in the art will recognize which materials will be utilized to prepare the desired intermediate or QLA according to the present invention. That is, the starting materials and resulting intermediates must be appropriately substituted to allow synthesis of the desired linking moiety.

The following general reaction schemes exemplify means for obtaining the various linking moieties described above. For each linking moiety, an exemplary reaction scheme is provided for making an intermediate of the formula (M - L^1) - L - (L^2 - B) (coupling step) and a QLA (the cyclization step).

For example, intermediates and QLAs having a carbamate linking moiety may be made according to the processes of the present invention as follows:

Step (1): (III)-NH + X-C(O)-O-CH_2-Lact ------>

(IV)-N-C(O)-O-CH_2-Lact

Step (2): Cyclize to yield Quin-N-C(O)-O-CH_2-Lact

where "(III)" represents a compound of Formula (III), which is described ab ve; "(IV)" represents a moiety of Formula (IV), which is described above; X is a reactive leaving group (such as alkoxy, halo, or N-heteroalkyl); "Lact" generically represents an appropriately protected lactam-containing structure (such as carbapenem, penem, cephem, monocyclic beta-lactam, oxacephem, r carbacephem); and "Quin" represents an appropriately protected quinolone. The sequence can be envisioned as formation of the intermediate lactam carbonate

derivative, followed by acylation of an amino functionality f a compound f Formula (III) t form a carbamate coupled lactam intermediate, followed by cyclization to form a carbamate-linked QLA.

When making carbamate-linked interemediates and QLAs, an optional step of reacting the compound of Formula (III) with an organosilicon compound may be performed prior to the coupling step (1). This step is illustrated in Examples 1 through 5 hereinbelow.

Alternatively, "reversed" carbamate linking-moieties can be prepared by the following sequence:

Step (1): (III)-$CH_2OC(=O)$-X + H_2N-CH_2-Lact →
Lact-CH_2-NHC(=O)O-CH_2-(IV)

Step (2): Cyclize to yield Lact-CH_2-NHC(=O)O-CH_2-Quin

where "(III)" represents a compound of Formula (III), which is described above; "(IV)" represents a moiety of Formula (IV), which is described above; X is a reactive leaving group (such as alkoxy, halo, or N-heteroaryl); "Lact" generically represents an appropriately protected lactam-containing structure (such as a penem, carbapenem, cephem, or carbacephem); and "Quin" represents an appropriately protected quinolone. The sequence can be envisioned as formation of a carbonate derivative of a compound of Formula (III), followed by acylation of a lactam amino functionality to form a carbamate coupled conjugate of the lactam intermediate (step(1)), followed by cyclization to form a reversed carbamate linked QLA.

Lactam-Quinolones having a dithiocarbamate linking moiety may be made by the following general reaction sequence:

Step (1): M^+-SC(=S)N-(III) + Lact-CH_2X →
Lact-CH_2-SC(=S)N-(IV)

Step (2): Cyclize to yield Lact-CH_2-SC(=S)N-Quin

where "(III)" represents a compound of Formula (III), which is described above; "(IV)" represents a moiety of Formula (IV), which is described above; X is a reactive leaving group (such as halo, a sulfonate ester, acetate, thiobenzoate or other activated hydroxyl functionality); "Lact" generically represents an appropriately protected lactam-containing structure (such as a penem, carbapenem, cephem, monocyclic beta-lactam, oxacephem, or carbacephem); and "Quin" represents an appropriately protected quinolone. The sequence can be envisioned as formation of a dithiocarbamate salt of a compound of Formula (III), followed by nucleophilic displacement of the lactam X substituent to form a dithiocarbamate coupled conjugate of the lactam intermediate (intermediate), followed by cyclization to yield a dithiocarbamate linked QLA.

Alternatively, "reversed" dithiocarbamate conjugates can be prepared by the

following sequence.

$$\text{Lact-CH}_2\text{-NH}_2 + \text{CS}_2 \rightarrow \text{Lact-CH}_2\text{-NHC(=S)S}^-\text{M}^+$$

Step (1): $\text{Lact-CH}_2\text{-NHC(=S)S}^-\text{M}^+ + \text{X-CH}_2\text{-(III)} \rightarrow \text{Lact-CH}_2\text{-NH C(=S)S-CH}_2\text{-(IV)}$

Step (2): Cyclize to give $\text{Lact-CH}_2\text{-NHC(=S)S-CH}_2\text{-Quin}$

where "(III)" represents a compound of Formula (III), which is described above; "(IV)" represents a moiety of Formula (IV), which is described above; X is a reactive leaving group (such as halo, a sulfonate ester or other activated hydroxyl functionality); "Lact" generically represents an appropriately protected lactam-containing structure (such as a penem, carbapenem, cephem, oxacephem, or carbacephem); and "Quin" represents an appropriately protected quinolone. The sequence can be envisioned as formation of the lactam dithiocarbonate salt, followed by nucleophilic displacement of the suitable compound (III) X substituent to form a "reversed" dithiocarbamate coupled conjugate of the lactam intermediate (step (1)), followed by cyclization to form a reverse dithiocarbamate-linked QLA.

Lactam-quinolones having a thiourea or urea linking moiety may be made by the following general reaction sequence:

$$\text{Lact-CH}_2\text{-X} + \text{M}^+\text{-YCN} \rightarrow \text{Lact-CH}_2\text{-N=C=Y}$$

Step (1) $\text{Lact-CH}_2\text{-N=C=Y} + \text{HN-(III)} \rightarrow \text{Lact-CH}_2\text{-NHC(=Y)N-(IV)}$

Step (2) Cyclize to yield $\text{Lact-CH}_2\text{NH(C=Y)N-Quin}$

(thiourea: Y=S; urea: Y=O)

where "(III)" represents a compound of Formula (III), which is described above; "(IV)" represents a moiety of Formula (IV), which is described above; X is a reactive leaving group (such as halo, a sulfonate ester, dichloroacetate, thiobenzoate or other activated hydroxyl functionality); and Y is either O r S. "Lact" generically represents an appropriately protected lactam-containing structure (such as a penem, carbapenem, cephem, monocyclic beta-lactam, oxacephem, r carbacephem), and "Quin" represents an appropriately protected quinolone. The sequence can be envisioned as formation of the intermediate lactam isothiocyanate (Y = S) or isocyanate (Y = O); followed by reaction with the amino substituent of a compound of Formula (III) to form a thiourea (Y = S) or urea (Y = O) coupled conjugate of the lactam and Formula III compound (intermediate) (step (1)), followed by cyclization to form a thiourea- (Y = S)- or urea- (Y = O) linked QLA.

Lactam-quinolones having an imine, amine or ammonium linking moiety may be made by the following general reaction sequence:

Step (1): $\text{Lact-CH}_2\text{HO} + \text{HN-(III)} \rightarrow \text{Lact-CH=N-(IV)}$ (an imine) $\rightarrow$

Lact-CH_2-N(R^{44})-(IV) (an amine) →
Lact-CH_2-N^+(R^{44})(R^{45})-(IV) (an ammonium)

Step (2): cyclization of the amine or ammonium intermediate to yield Lact-CH=N-Quin, Lact-CH_2-N(R^{44})-Quin or Lact-CH_2-N^+(R^{44})(R^{45})-Quin, respectively

where "(III)" represents a compound of Formula (III), which is described above; "(IV)" represents a moiety of Formula (IV), which is described above; R^{44} and R^{45} are described above; "Lact" generically represents an appropriately protected lactam-containing structure (such as a penem, carbapenem, cephem, oxacephem, or carbacephem; and "Quin" represents an appropriately protected quinolone. The sequence can be envisioned as the condensation of the amine of a compound of Formula (III) with the lactam aldehyde to form the imine coupled lactam intermediate conjugate. Reduction of the imine yields the corresponding amine coupled lactam intermediate conjugate. Alkylation yields the corresponding quaternary ammonium-coupled lactam intermediate conjugate. Cyclization of the desired intermediate will yield an imine-, amine-, or ammonium-linked QLA.

Lactam-quinolones having an amine linking moiety may alternatively be made by the following general reaction sequence:

Step (1): Lact-CH_2X + HN-(III) → Lact-CH_2-N(R^{44})-(IV) (an amine) →

Step (2): cyclization of the amine to yield Lact-CH_2-N(R^{44})-Quin

where "(III)" represents a compound of Formula (III), which is described above; "(IV)" represents a moiety of Formula (IV), which is described above; R^{44} and R^{45} are described above; "Lact" generically represents an appropriately protected lactam-containing structure (such as a penem, carbapenem, cephem, oxacephem, or carbacephem; X is a leaving group described above and "Quin" represents an appropriately protected quinolone.

Alternatively, the quaternary ammonium conjugate can be prepared by the following general sequence.

Step (1): Lact-CH_2-X + (R^{44})(R^{45})N-(III) →
Lact-CH_2-N^+(R^{44})(R^{45})-(IV)

Step (2): Cyclize to yield Lact-CH_2-N^+(R^{44})(R^{45})-Quin

where "(III)" represents a compound of Formula (III), which is described above; "(IV)" represents an intermediate compound of Formula (IV), which is described above; R^{44} and R^{45} are described above; X is a reactive leaving group (such as halo, a sulfonate ester, or other activated hydroxyl functionality, etc.). This sequence can be envisioned as a quaternization of a tertiary amino gr up of a compound of Formula (III) with the lactam material to obtain the quaternary ammonium coupled conjugate between the lactam and compound of Formula (III)

(step (1)), followed by cyclization to form the ammonium-linked QLA.

Lactam-quinolones having an amide linking moiety may be made by the following general sequence:

Step (1): Lact-CH_2-NH_2 + X-C(=O)-(III) →

Lact-CH_2-NHC(=O)-(IV)

Step (2): Cyclize to yield Lact-CH_2-NHC(=O)-Quin

where "(III)" represents a compound of Formula (III), which is described above; "(IV)" represents an intermediate compound of Formula (IV), which is described above; X is a reactive leaving group (such as halo, an HOBt ester, mixed anhydride or other activated carboxyl functionality); "Lact" generically represents an appropriately protected lactam-containing structure (such as a penem, carbapenem, cephem, oxacephem, or carbacephem); and "Quin" represents an appropriately protected quinolone. The reaction can be envisioned as an acylation of the lactam amino substituent with the activated carboxyl group of a compound of Formula (III), to form an amide coupled conjugate of the lactam and Formula (III) compound (intermediate), followed by cyclization to form the amide-linked QLA.

Lactam-quinolones having a guanidinium linking moiety may be made by the following general reaction sequence:

$H_2NC(=S)N$-(III) → RSC(=NH_2^+X)N-(III)

Step (1): RSC(=$NH_2^+X^-$)N-(III) + Lact-CH_2-NH_2 →

Lact-CH_2-NHC(=$NH_2^+X^-$)N-(IV)

Step (2): Cyclize to yield Lact-CH_2-NHC(=$NH_2^+X^-$)N-Quin

where "(III)" represents a compound of Formula (III), which is described above; "(IV)" represents an intermediate compound of Formula (IV), which is described above; "Lact" generically represents an appropriately protected lactam-containing structure (such as penem, carbapenem, cephem, oxacephem, or carbacephem): and "Quin" represents an appropriately protected quinolone. The sequence can be envisioned as formation of the isothiouronium salt of a compound of Formula (III), followed by reaction with the lactam amino substituent to form a guanidinium coupled conjugate of the lactam and compound of Formula (III) (intermediate), followed by cyclization to form a guanidinium-linked QLA.

Lactam-quinolones having a heteroarylium linking moiety may be made by the following general reaction sequence:

Step (1): Lact-CH_2-X + N_{Het}-(III) →

Lact-CH_2-N^+_{Het}-(IV)

Step (2): Cyclize to yield Lact-$CH_2N^+_{Het}$-Quin

where "(III)" represents a compound of Formula (III), which is described above; "(IV)" represents an intermediate compound of Formula (IV), which is d scribed

above; X is a reactive leaving group (such as halo, a sulfonate ester, acetate, thiobenzoate or other activated hydroxyl functionality); "N_{Het}" is an heteroaryl moiety, N^{+}_{Het} is a heteroaryl having a ring quaternary nitrogen atom, "Lact" generically represents an appropriately protected lactam-containing structure (such as a penem, carbapenem, cephem, monocyclic beta-lactam, oxacephem, r carbacephem); and "Quin" represents an appropriately protected quinolone that contains a heteroaromatic nitrogen-containing substituent (for example, pyridine). The sequence can be envisioned as an alkylation of the heteroaromatic nitrogen-containing substituent of a compound of Formula (III) by the lactam to form the pyridinium-type conjugate (intermediate), followed by cyclization to form the pyridinium-linked QLA.

Lactam-quinolones having a xanthate linking moiety may be made by the following general reaction sequence:

Step (1): $M^{+-}SC(=S)O$-(III) + Lact-CH_2-X →
Lact-CH_2-SC(=S)O-(IV)

Step (2): Cyclize to form Lact-CH_2-SC(=S)O-Quin

where "(III)" represents a compound of Formula (III), which is described above; "(IV)" represents an intermediate compound of Formula (IV), which is described above; X is a reactive leaving group (such as halo, a sulfonate ester, acetate, thiobenzoate or other activated hydroxyl functionality); "Lact" generically represents an appropriately protected lactam-containing structure (such as a penem, carbapenem, cephem, monocyclic beta-lactam, oxacephem, or carbacephem); and "Quin" represents an appropriately protected quinolone. The sequence can be envisioned as formation of the xanthate salt of a compound of Formula (III), followed by nucleophilic displacement of the lactam X substituent to form a xanthate coupled conjugate of the lactam and Formula (III) compound (intermediate), followed by cyclization to yield the xanthate-linked QLA.

Lactam-quinolones having a thioether, sulfoxide or sulfone linking moiety may be made by the following general reaction sequence:

Step (1): Lact-CH_2-X + HS-(III) → Lact-CH_2-S-(IV) (a thioether) →
Lact-CH_2-SO-(IV) (a sulfoxide) →
Lact-CH_2SO_2-(IV) (a sulfone)

Step (2): Cyclization of the thioether, sulfoxide or sulfone to form
Lact-CH_2-S-Quin, Lact-CH_2-SO-Quin, or
Lact-CH_2-SO_2-Quin, respectively

where "(III)" represents a compound of Formula (III), which is described above; "(IV)" represents an intermediate compound of Formula (IV), which is described above; X is a reactive leaving group (such as halo, a sulfonate ester, acetate,

thiobenzoate or other activated hydroxyl functionality, etc.); "Lact" generically represents an appropriately protected lactam-containing structure (such as a penem, carbapenem, cephem, monocyclic beta-lactam, oxacephem, or carbacephem); and "Quin" represents an appropriately protected quinolone. The sequence can be envisioned as nucleophilic displacement of the lactam X group with a thio-containing compound of Formula (III) to form the thioether coupled conjugate (intermediate). Oxidation of the thioether yields the corresponding sulfoxide conjugate. Further oxidation produces the sulfone lactam intermediate conjugate. Cyclization of the thioether, sulfoxide, or sulfone intermediate will form a thioether-linked, a sulfoxide-linked, or sulfone-linked QLA, respectively.

Lactam-quinolones having an isothiouronium linking group may be made by the following general reaction sequence:

$$RC(=O)N=C=S + HN\text{-(III)} \rightarrow H_2NC(=S)N\text{-(III)}$$

Step (1): $H_2NC(=S)N\text{-(III)} + \text{Lact-}CH_2\text{-}X \rightarrow \text{Lact-}CH_2\text{-}SC(=NH_2^+X^-)N\text{-(IV)}$

Step (2): Cyclize to give $\text{Lact-}CH_2\text{-}SC(CNH_2^+X^-)N\text{-Quin}$

where "(III)" represents a compound of Formula (III), which is described above; "(IV)" represents an intermediate compound of Formula (IV), which is described above; X is a reactive leaving group (such as halo, a sulfonate ester, acetate, thiobenzoate or other activated hydroxyl functionality); "Lact" generically represents an appropriately protected lactam-containing structure (such as a penem, carbapenem, cephem, monocyclic beta-lactam, oxacephem, or carbacephem; and "Quin" represents an appropriately protected quinolone. The sequence can be envisioned as formation of the thiourea-containing compound of Formula (III), followed by nucleophilic displacement of the lactam X substituent to f rm a isothiouronium coupled conjugate (intermediate), followed by cyclization to QLA.

In the reaction sequences described herein, certain functional groups contained in the Lact, (III) and (IV) structures, (such as carboxyl, hydroxyl, and amino groups) may need to be in a protected form. If various protecting groups are employed, then appropriate deprotecting chemistry, that will not decompose the coupled conjugate, may be required to obtain antibacterially active products. Depending on the R^{10} group desired, the lactam starting material may be available from any of a variety of commercial sources. Synthetic methods for producing such lactams are well-known in the chemical literature. See, for example, Antibiotics, Chemotherapeutics, and Antibacterial Agents for Disease Control, pages 107-125 (M. Grayson, editor, 1982), inc rporated by referenc herein.

Preferably, the processes of the present invention additionally comprise

steps for protecting the lactam and compound of Formula (III) prior to the coupling step. In particular, the carboxylate groups at R^4 and R^{13} are in a protected form, using, for example, an ester group.

Alternatively, the compound may be further reacted to form another QLA moiety that is known to have antimicrobial activity. For example, the QLA may be further reacted to yield a compound where A^1 is $-C(R^7)-$ and R^7 and R^1 together comprise a heterocylic 6-membered, oxygen- (pyridobenzoxazine) or sulfur- (pyridobenzthiazine) contaning ring including N' and A^1.

A preferred process of this invention additionally comprises:

(a) a step, prior to said coupling step, wherein a compound of Formula (II), a compound of Formula (III), or both are protected; and

(b) deprotection steps, after said cyclization step, wherein the protecting groups are removed.

The coupling step is carried out in solution, using any of a variety of suitable solvents. Such solvents include, for example: halocarbon solvents, such as methylene chloride, chloroform, and dichloroethane; ethers, such as diethyl ether and tetrahydrofuran (THF); aromatic solvents, such as benzene and toluene; dialkylamides, such as N,N-dimethylformamide; or mixtures thereof.

In particular, in the formation of carbamate linkages, halocarbon solvents are preferred. Most preferred is methylene chloride and dichloromethane.

In particular, in the formation of amine linkages, halocarbon and dialkylamides and mixtures thereof are preferred. More preferred is dichloroethane or dichloromethane, and N,N-dimethylformamide, or mixtures thereof. Most preferred is a mixture of dichloroethane or dichloromethane, and N,N-dimethylformamide.

In coupling reactions wherein an organosilicon compound is employed, the coupling step is preferably conducted at temperatures less than about 0°C. Preferably the temperatures are from about -78°C to about -15°C, more preferably from about -20°C to about -15°C. Preferably, reagents are mixed in the coupling step so as to allow control of the temperature within these ranges.

In coupling reactions wherein an organosilicon compound is not employed, the coupling step is preferably conducted at temperatures from about -78°C to about 50°C. More preferably the temperatures are from about -50°C to about 25°C; even more preferably from about -20°C to about 0°C. Preferably, reagents are mixed in the coupling step so as to allow control of the temperature within these ranges.

Methods for the cyclization of quinolone precursors, including the intermediates of the present invention, to yield QLAs (and quinolones generally) is specifically described and claimed in co-pending application Serial No. __, filed

August 2, 1994, by Randall, et al. The cyclization step is carried out in a mixture of the substrate and one or more of a variety of known solvents. Such solvents include, but are not limited to: halocarbon solvents, such as methylene chloride, chloroform, and dichloroethane; ethers, such as diethyl ether and tetrahydrofuran (THF); aromatic solvents, such as benzene and toluene; alkyl nitriles, such as acetonitrile; and mixtures thereof. Halocarbon, ether, and alkyl nitrile solvents are preferred. More preferred solvents include methylene chloride, THF, acetonitrile, or mixtures thereof. The cyclization reaction (step (2)) is carried out at a temperature sufficient to effect cyclization of the intermediate compound formed in the coupling step). The cyclization reaction is preferably carried out at temperatures greater than -15°C. More preferred is where the reaction is conducted at temperatures from about 0°C to about 110°C. Most preferred reaction temperatures are from about 25°C to about 50°C. Preferably, reagents are mixed in the reaction step so as to allow control of the temperature within these ranges. Preferably, from about 1 to about 14 mole equivalents of the silyl-containing compound will be added for each mole of the intermediate compound (i.e., a mole ratio of organosilicon compound t intermediate of from about 1:1 to about 14:1). More preferred is a mole ratio of from about 2:1 to about 12:1. Most preferred is a mole ratio of about 2:1 to about 6:1.

Procedures for making a variety of lactam and Formula (III) starting materials are well known in the art. For example, procedures for preparing lactam-containing moieties are described in the following references, all incorporated by reference herein (including articles cited within these references): Cephalosporins and Penicillins: Chemistry and Biology (E. H. Flynn, ed, 1972) Chapters 2, 3, 4, 5, 6, 7, 15 and Appendix I; Recent Advances in the Chemistry of b-Lactam Antibiotics (A.G. Brown and S. M. Roberts, ed., 1985); Topics in Antibiotic Chemistry, Vol. 3, (Part B) and Vol. 4, (P. Sommes, ed., 1980); Recent Advances in the Chemistry of b-lactam Antibiotics (J. Elks, ed., 1976); Structure-Activity Relationships Among the Semisynthetic Antibiotics (D. Perlman, ed, 1977); Chapts. 1, 2, 3, 4; Antibiotics, Chemotherapeutics and Antibacterial Agents for Disease Control (M. Grayson, ed, 1982); Chemistry and Biology of b-Lactam Antibiotics, Vols 1-3 (K. B. Morin and M. Gorman, eds, 1982); 4 Medicinal Research Reviews 1-24 (1984); 8 Medicinal Research Review 393-440 (1988); 24 Angew. Chem. Int. Ed. Engl. 180-202 (1985); 40 J. Antibiotics 182-189 (1987); European Patent Publication 266,060; 42 J. Antibiotics 993 (1989); U.S. Patent 4,742,053; 35 Chem. Pharm. Bull. 1903-1909 (1987); 32 J. Med. Chem., 601-604 (1989); U.S. Patent 4,791,106; Japanese Patent Publication 62/158291; 31 J. Med. Chem. 1987-1993 (1988); 30 J. Med. Chem., 514-522 (1987); 28 Tet. Let. 285-288 (1987); 28 Tet.

Let. 289-292 (1987); 52 J. Org. Chem., 4007-4013 (1987); 40 J. Antibiotics, 370-384 (1987); 40 J. Antibiotics, 1636-1639 (1987); 37 J. Antibiotics, 685-688 (1984); 23 Heterocycles, 2255-2270; 27 Heterocycles, 49-55; 33 Chem. Pharm. Bull. 4371-4381 (1985); 28 Tet. Let, 5103-5106 (1987); 53 J. Org. Chem., 4154-4156 (1988); 39 J. Antibiotics, 1351-1355 (1986); 59 Pure and Appl. Chem., 467-474 (1987); 1987 J.C.S. Chem. Comm.; 44 Tetrahedron, 3231-3240 (1988); 28 Tet. Let., 2883-2886, (1987); 40 J. Antibiotics, 1563-1571 (1987); 33 Chem. Pharm. Bull., 4382-4394 (1985); 37 J. Antibiotics, 57-62 (1984); U.S. Patent 4,631,150; 34 Chem. Pharm. Bull., 999-1014 (1986); 52 J. Org. Chem., 4401-4403 (1987); 39 Tetrahedron, 2505-2513 (1983); 38 J. Antibiotics, 1382-1400 (1985); European Patent Application 053,815; 40 J. Antibiotics, 1563-1571 (1987); 40 J. Antibiotics, 1716-1732 (2987); 47 J. Org. Chem., 5160-5167 (1981); U.S. Patent 4,777,252; U.S. Patent 4,762,922; European Patent Publication 287,734; U.S. Patent 4,762,827; European Patent Publication 282,895; European Patent Publication 282,365; and U.S. Patent 4,777,673.

General procedures for preparing compounds of Formula (III) follow the reaction scheme for preparing the related quinolone, with the exception that the final cyclization step known in the art (affected by a strong base) is not performed. Such methods are described in the following references, all incorporated by reference herein (including articles listed within these references): U.S. Patent No. 5,140,033, issued August 18, 1992 to Schriewer et al.; U.S. Patent N . 4,886,810, issued December 12, 1989 to Matsumoto et al.; U.S. Patent N . 4,885,386, issued December 5, 1989 to Wemple et al.; U.S. Patent N . 4,684,648, issued August 4, 1987 to Tone et al.; European Patent Publication 522,277, Cecchetti et al., published January 13, 1993; European Patent Publication 470,578, Yokomoto et al., published February 12, 1992; Europeant Patent Publication 319,906, Matsumoto et al., published June 14, 1989; Europeant Patent Publication 287,951, Ueda et al., published October 26, 1988; Europeant Patent Publication 195,316, Irikura et al., published March 6, 1986; German Patent Publication DE-3702393, Schwiewer et al., published August 11, 1988; German Patent Publication DE-3641312, Preiss, published June 9, 1988; German Patent Publication DE-3601567, Petersen et al., published July 23, 1987; German Patent Publication DE-3600891, Schriewer et al., published July 16, 1987; German Patent Publication DE-3504643, Petersen et al., August 14, 1986; German Patent Publication DE-3420743, Petersen et al., published December 5, 1985; Japanese Patent Publication JP/02215749, Furumiya et al., published August 28, 1990; Japanese Patent Publication JP/60172981, Hayakawa, published September 6, 1985; World Patent Publication 92/03136, Chu et al., published March 5, 1992;

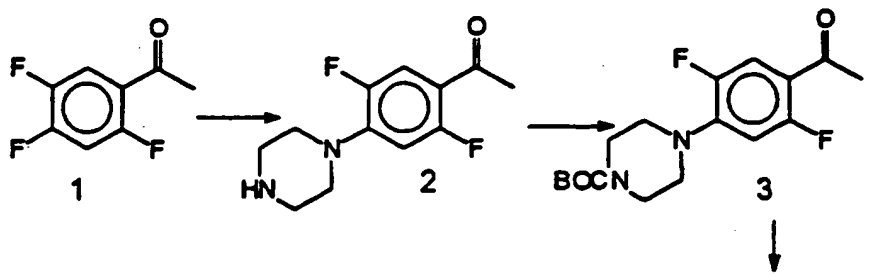
W rld Patent Publication 89/06649, Domagalia et al., published July 27, 1989; Chu et al., "An Alternative Synthesis of Temafloxacin, a Potent Antibacterial Agent", 70(5) Can. J. Chem. 1323-27 (1992); Remuzon, "Fluoronaphthyridines and Quinolones as Antibactertial Agents", 34(1) J. Med. Chem. 29-37 (1991); Cecchetti et al., "One-pot Synthesis of Rufloxacin", 21(22) Synth. Commun. 2301-08 (1991); Chu et al., "Synthesis of 4-oxo-4H quino[2,3,4-i,j][1,4]benoxazine-5-carboxylic Acid Derivatives", 24(2) J. Hetercycl. Chem. 453-456 (1987); Egawa et al., "A New Synthesis of 7H-Pyrido[1,2,3,-de][1,4]benzoxazine Derivatives Including an Antibacterial Agent, Ofloxacin", 34(10) Chem. Pharm. Bull. 4098-4102 (1986).

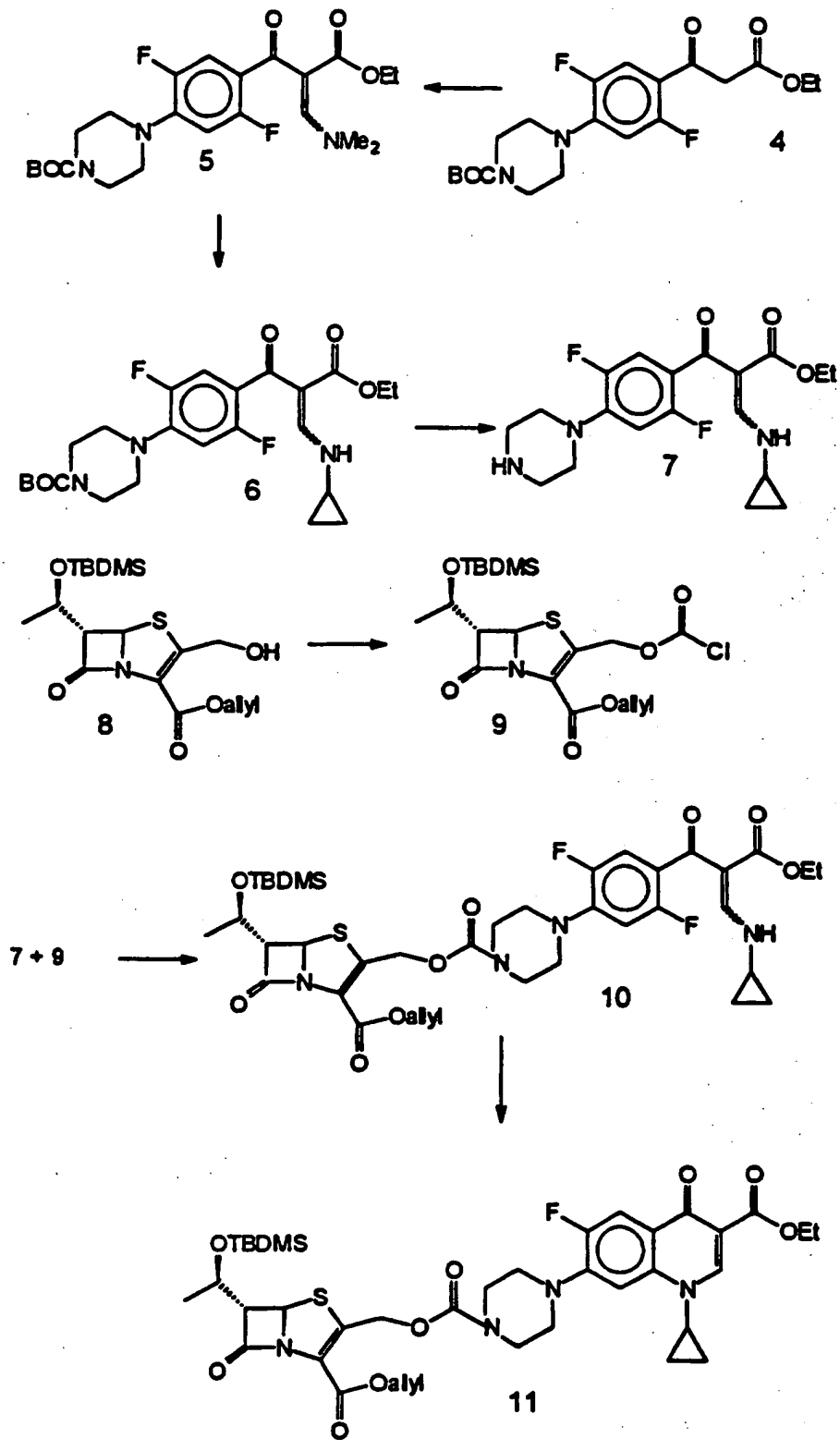
Additional references describing methods for preparing the compounds of Formula (II) are described in the following references, all incorporated by reference herein (including articles listed within these references): 31 J. Med. Chem., 503-506 (1988); 32 J. Med. Chem., 1313-1318 (1989); 1987 Liebigs Ann. Chem., 871-879 (1987); 14 Drugs Exptl. Clin. Res., 379-383 (1988); 31 J. Med. Chem., 983-991 (1988); 32 J. Med. Chem., 537-542 (1989); 78 J. Pharm. Sci., 585-588 (1989); 26 J. Het. Chem., (1989); 24 J. Het. Chem., 181-185 (1987); U.S. Patent 4,599,334; 35 Chem. Pharm. Bull., 2281-2285 (1987); 29 J. Med. Chem., 2363-2369 (1986); 31 J. Med. Chem., 991-1001 (1988); 25 J. Het. Chem., 479-485 (1988); European Patent Publication 266,576; European Patent Publication 251,308, 36 Chem. Pharm. Bull., 1223-1228 (1988); European Patent Publication 227,088; European Patent Publication 227,039; European Patent Publication 228,661; 31 J. Med. Chem., 1586-1590 (1988); 31 J. Med. Chem., 1598-1611 (1988); 23 J. Med. Chem., 1358-1363 (1980); 21 Progress in Drug Research, 9-104 (1977).

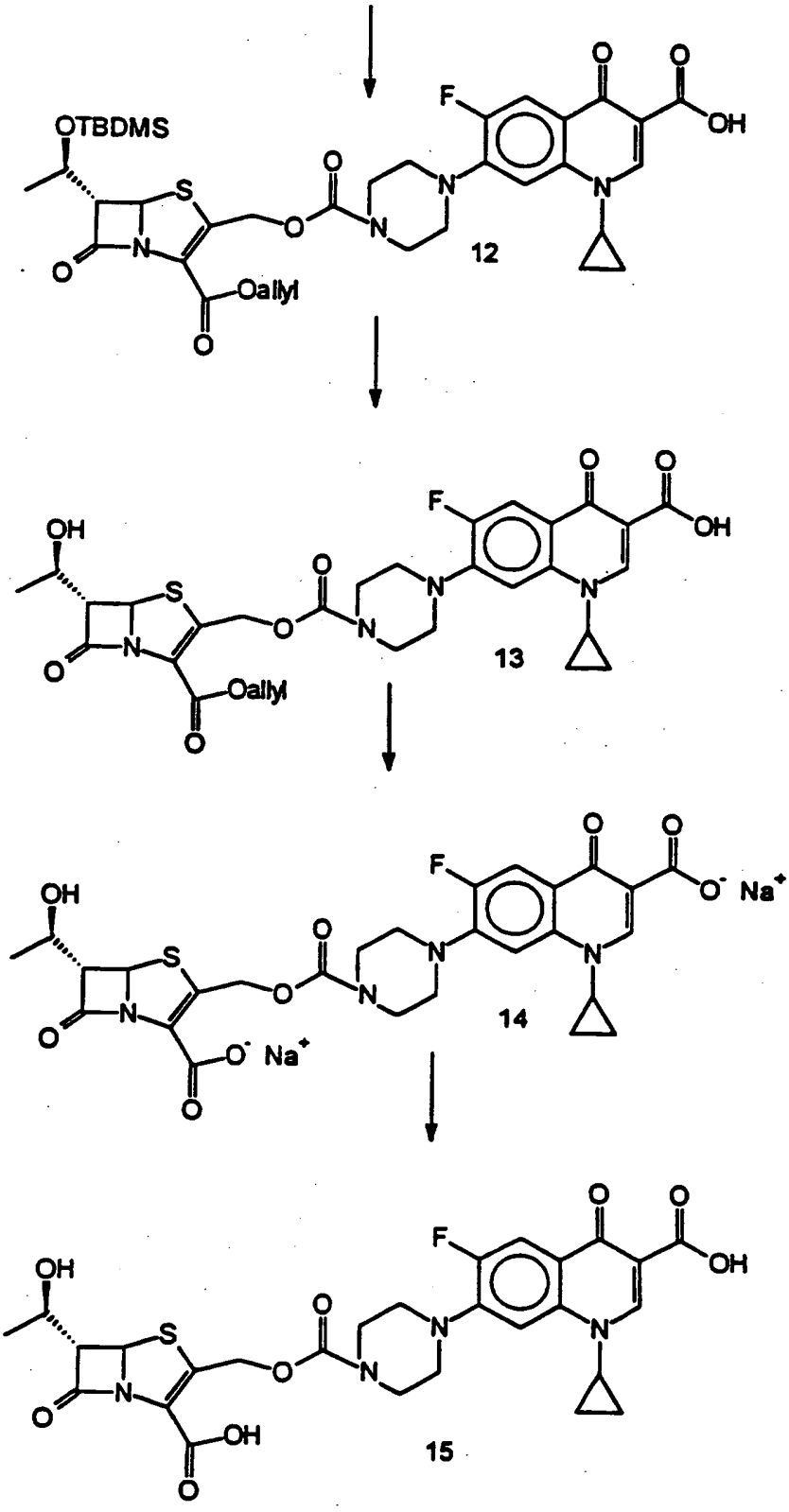
The following non-limiting examples illustrate the processes of the present invention.

EXAMPLE 1

Synthesis of [5R-[5α,6α(R*)]]-3-[[[4-(3-Carboxy-1-cyclopropyl-6-flu ro-1,4-dihydro-4-oxo-7-quinolinyl)-1-piperazinyl]carbonyloxy]methyl]-6-(1-hydr xy-ethyl)-7-oxo-4-thia-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid.




F
O
OEt
NMe2
BOCN
5
4
6
NH
7
HN
OTBDMS
S
OH
N
Oallyl
8
Cl
9
7 + 9
10
11


OTBDMS
Oallyl
12
OH
Oallyl
13
OH
Na+
14
OH
OH
15

T a solution of 2,4,5-trifluoroacetophenone (15.0 g) (Compound 1) in THF (300 mL) is added piperazine (29.6 g). The mixture is refluxed under N_2 for 1 hour and the THF is removed under reduced pressure. The residue is slurried in EtOAc (150 mL), and the excess piperazine is filtered off and rinsed with EtOAc. The EtOAc filtrate is washed with water (2 x 150 mL) and the combined aqueous layers are extracted with EtOAc (75 mL). The combined EtOAc layers are dried ($MgSO_4$) and treated with activated charcoal. The solvents are evaporated in vacuo and the residue is crystallized from isopropyl ether to give Compound 2.

To a solution of Compound 2 (9.4 g) in $CHCl_3$ (141 mL) is added a solution of di-t-butylcarbonate (9.39 g) in $CHCl_3$ (50 mL). The reaction is stirred for 5 minutes under N_2 at ambient temperature and evaporated in vacuo. Hexanes are added to give Compound 3.

To a cooled solution of Compound 3 (10.0 g) in THF (100 mL) under N_2 at 0-5°C is added a 60% oil immersion of NaH (2.5 g), portionwise. The reaction mixture is stirred for 15 minutes and diethylcarbonate (14.2 mL) is added. The reaction is stirred for 18 hours under N_2 at ambient temperature and quenched with a 28:1 mixture of water and HOAc (100 mL). The organic portion is evaporated in vacuo and the residue is subjected to column chromatography (silica, 10:89:1% EtOAc/Hexane/HOAc). The residue is crystallized from hexanes to give Compound 4.

To a solution of Compound 4 (11.95 g) in toluene (47.8 mL) is added dimethylformamide dimethylacetal (5.95 mL). The reaction is heated to reflux f r 20 hours under N_2 and concentrated in vacuo to obtain Compound 5. Compound 5 is carried directly to the next step by dissolving in EtOH (47.8 mL) and adding cyclopropyl amine (3.2 mL). The mixture is stirred for 2 hours at ambient temperature under N_2. The volatiles are removed in vacuo and the residue is crystallized from 20% EtOAc/hexanes to give Compound 6.

To a cooled solution of Compound 6 (12.06 g) in anisole (97.7 mL) at 5-10°C is added trifluoroacetic acid (TFA) (97.7 mL). After stirring for 5 minutes under N_2, the ice bath is removed and the reaction is warmed to ambient temperature. After 2 hours, most of the TFA and some of the anisole is removed in vacuo. The residue is slurried in Et_2O (300 mL) and filtered. The solid is dissolved in a mixture of CH_2Cl_2 (100 mL) and saturated $NaHCO_3$ (100 mL) and stirred for 10 min. The CH_2Cl_2 portion is separated, dried ($MgSO_4$), treated with activated charcoal, and evaporated in vacuo. The residue is crystallized with hexane to give the mono-hydrate of Compound 7.

A solution of Compound 7 (2.1 g) in CH_2Cl_2 (50 mL) is dried (Na_2SO_4) and the dried solution is transferred to a second vessel, under N_2. The solution is

cooled (-15°C) and N,O-bis(trimethylsilyl)acetamide (2.7 mL) is added. The mixture is allowed to stir for 15 minutes under N_2 to yield a silylated form of Compound 7, which is used without further characterization.

In a third vessel, a solution of Compound 8 (2.06 g) in CH_2Cl_2 (50 mL) prepared according to U.S. Patent 4,631,150, Battistini et al., issued December 23, 1986 (incorporated by reference herein), is dried (Na_2SO_4) and the dried solution is transferred to a fourth vessel, under N_2. N,N-diisopropylethylamine (1.05 mL) is added and the solution is stirred for 15 minutes at ambient temperature, under N_2, and cooled to -78°C. In a fifth vessel, to cooled (-78°C) CH_2Cl_2 (40 mL) is added 20% phosgene in toluene (3.45 mL) under N_2. The forementioned soluti n of Compound 8 is added dropwise while maintaining the solution temperature at less than -60°C. The reaction is stirred for 15 minutes and warmed to -15°C to provide Compound 9, which is then reacted in situ by dropwise addition of the forementioned solution of Compound 7, while maintaining the temperature below -15°C. The reaction is stirred at -15°C under N_2 until complete. The reacti n mixture is quenched with water (160 mL), warmed to 0°C and stirred 10 minutes. The organic portion is separated and dried with (Na_2SO_4). The volatiles are evaporated in vacuo and the residue is subjected to column chromatography (silica) to give Compound 10.

To a solution of Compound 10 (1.2 g) in CH_3CN (21 mL) is added BTMSA (1.09 mL). The reaction mixture is stirred under N_2 at ambient temperature until complete. The reaction is quenched with water (21 mL), and the resulting slurry is filtered and washed with a mixture of water and CH_3CN (5:1) to provide Compound 11.

To a solution of Compound 11 (1.1 g) in benzene (25 mL) is added bis(tributyltin) oxide (1.43 mL), under N_2. The mixture is heated to reflux until completion, whereupon the volatiles are removed in vacuo and the residue obtained is subjected to column chromatography (silica) to provide Compound 12.

To a solution of Compound 12 (0.9 g) in THF (8 mL) and acetic acid (0.62 mL) is added tetra-n-butyl ammonium fluoride (3.21 mL of a 1M solution in THF), under N_2. The mixture is stirred at ambient temperature overnight and, up n completion, is diluted with ether (15 mL). The solution is stirred for a half-hour, allowing the product to crystallize. The slurry is filtered through troyfelt and the solid residue is washed with ether to obtain Compound 13.

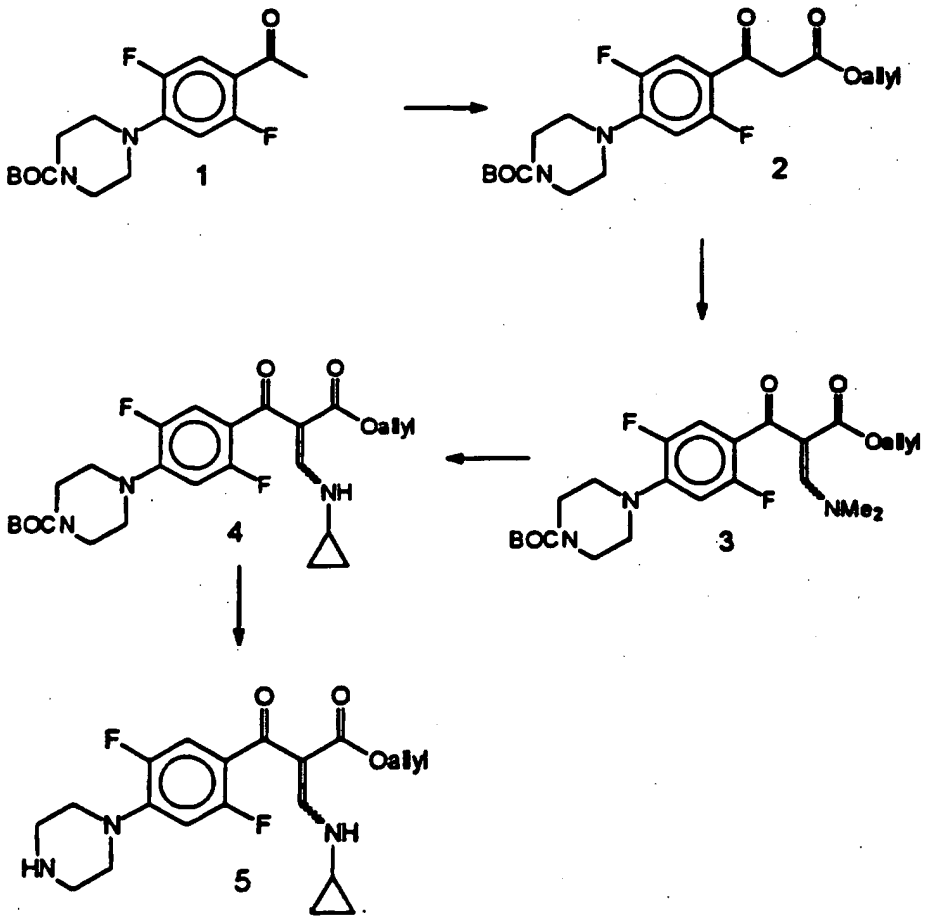
To a solution of Compound 13 (0.75 g) in CH_2Cl_2 (45 mL) is added tetrakis(triphenylphosphine)palladium (0) (135 mg), under N_2. The mixture is cooled (-10 t -5°C) and a cooled solution (<-10°C) of sodium ethylhexan ate (389 mg) in THF (22 mL) is added dropwise. The mixture is stirred f r

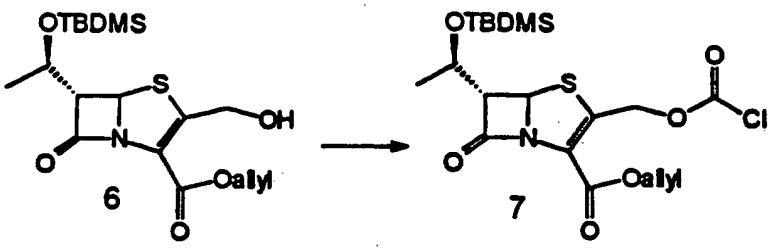
approximately 30 minutes, whereupon the resulting slurry is filtered and washed successively with CH_2Cl_2 and acetone, to obtain Compound 14.

To a solution of Compound 14 (0.55 g) in absolute ethanol (77 mL) is added highly acidic ion-exchange resin (1.1 g, Amberlite IR-120 - plus), under N_2. The mixture is stirred at ambient temperature for approximately 5 hours, whereupon it is filtered through a sintered glass filtration funnel to remove the resin. The filtrate is reduced in vacuo to approximately one third of its volume, whereupon water (27 mL) is added. The mixture is stirred for a few minutes and then filtered. The solid obtained is washed with water and dried in vacuo overnight to obtain [5R-[5α,6α(R*)]]-3-[[[4-(3-Carboxy-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-quinolinyl)-1-piperazinyl]carbonyloxy]methyl]-6-(1-hydroxyethyl)-7-oxo-4-thia-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid (Compound 15).

EXAMPLE 2

Synthesis of [5R-[5α,6α(R*)]]-3-[[[4-(3-Carboxy-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-quinolinyl)-1-piperazinyl]carbonyloxy]-methyl]-6-(1-hydroxyethyl)-7-oxo-4-thia-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid.





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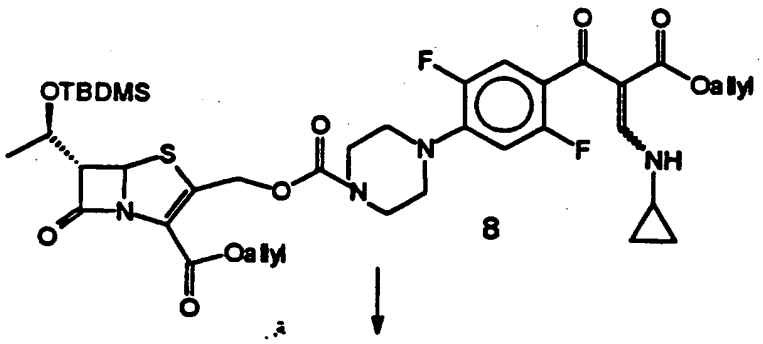
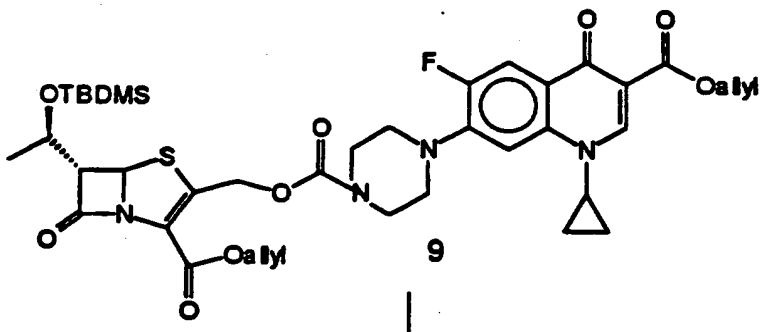
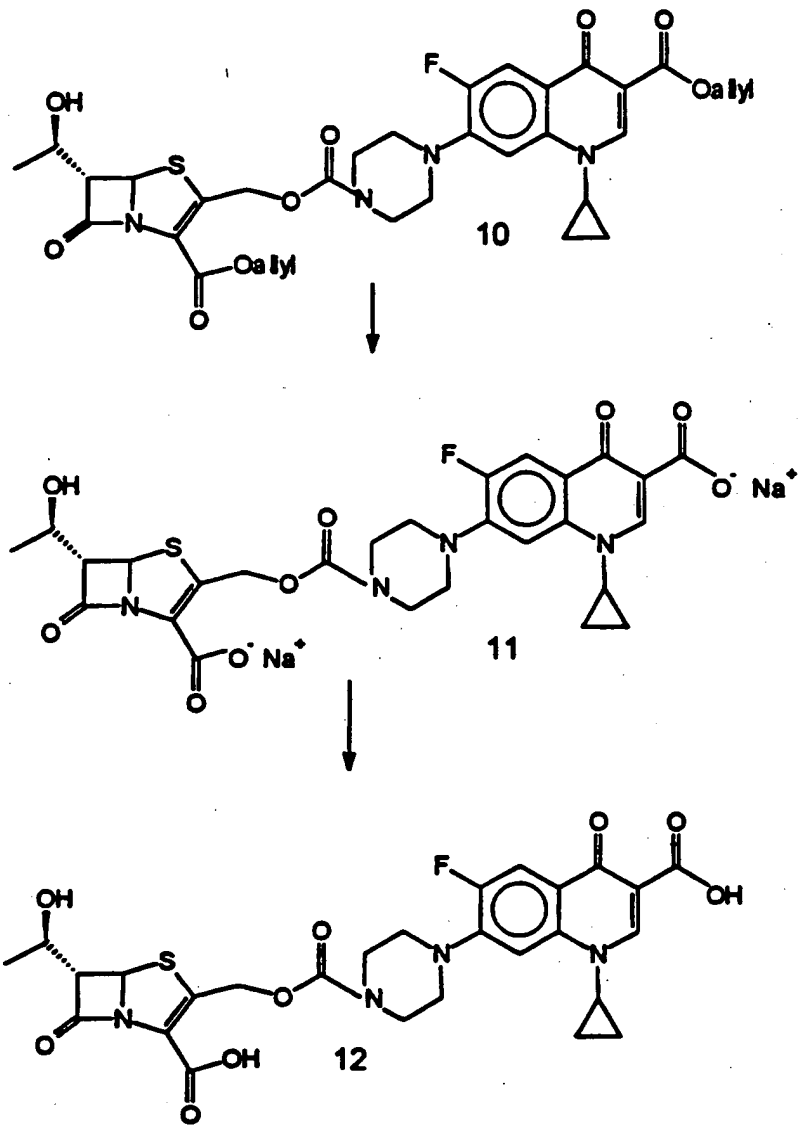






To a cooled solution of Compound 1 (10.0 g) (prepared in the same manner as Compound 3 in Example 1) in THF (100 mL) under N_2 at 0-5°C is added a 60% oil immersion of NaH (2.5 g), portionwise. The reaction mixture is stirred for 15 minutes and diallylcarbonate (16.9 mL) is added. The reaction is stirred for 18 hours under N_2 at ambient temperature and quenched with a 28:1 mixture of water and HOAc (100 mL). The organic portion is evaporated in vacuo and the residue is subjected to column chromatography (silica). The residue is crystallized from hexanes to give Compound 2.

To a solution of Compound 2 (10.5 g) in toluene (42 mL) is added dimethylformamide dimethylacetal (5.1 mL). The reaction is heated t reflux f r 20 hours under N_2 and concentrated in vacuo to obtain Compound 3. Compound 3 is carried directly to the next step by dissolving in EtOH (42 mL) and adding

cyclopropylamine (2.73 mL). The mixture is stirred for 2 hours at ambient temperature under N_2. The volatiles are removed in vacuo and the residue is crystallized from 20% EtOAc/hexanes to give Compound 4.

To a cooled solution of Compound 4 (9.75 g) in anisole (79 mL) at 5-10°C is added TFA (79 mL). After stirring for 5 minutes under N_2, the ice bath is removed and the reaction is warmed to ambient temperature. After 2 hours, most of the TFA and some of the anisole is removed in vacuo. The residue is slurried in Et_2O (250 mL) and filtered. The solid is dissolved in a mixture of CH_2Cl_2 (80 mL) and saturated $NaHCO_3$ (80 mL) and stirred for 10 min. The CH_2Cl_2 portion is separated, dried ($MgSO_4$), treated with activated charcoal, and evaporated in vacuo. The residue is crystallized from hexanes to give Compound 5.

To a solution of Compound 5 (2.2 g) in CH_2Cl_2 (55 mL) is added activated molecular sieves (400 mg). The solution is transferred to a second vessel, under N_2, and cooled (-15°C). N,O-Bis(trimethylsilyl)acetamide (2.75 mL) is added and the mixture is allowed to stir for 15 minutes. Concurrent with this procedure, Compound 6 (2.09 g), prepared according to U. S. Patent 4,631,150, Battistini et al., issued December 23, 1986 (incorporated by reference herein), is dissolved in CH_2Cl_2 (55 mL) in a third vessel and activated 4A molecular sieves (500 mg) are added, under N_2. After stirring for 30 minutes, the solution is transferred via canula to a fourth vessel and N,N-diisopropylethylamine (1.08 mL) is added under N_2. The solution is stirred for 15 minutes at ambient temperature and cooled to -78°C. In a fifth vessel, to cooled (- 78°C) CH_2Cl_2 (45 mL) is added 20% phosgene in toluene (3.5 mL) under N_2. The forementioned solution of Compound 6 is added dropwise while maintaining the solution temperature at less than -60°C. The reaction is stirred for 15 minutes and warmed to -15°C to provide Compound 7 which is then reacted in situ by dropwise addition of the forementioned solution of Compound 5, while maintaining the temperature below -15°C. The reacti n is stirred at -15°C under N_2 until complete. The reaction mixture is quenched with water (30 mL), warmed to 0°C and stirred 10 minutes. The organic portion is separated and dried with (Na_2SO_4). The volatiles are evaporated in vacuo and the residue is subjected to column chromatography (silica) to give Compound 8.

To a solution of Compound 8 (2.1 g) in CH_3CN (30 mL) is added BTMSA (1.89 mL). The reaction mixture is stirred under N_2 at ambient temperature until complete. The reaction is quenched with water (30 mL), and the resulting slurry is filtered and washed with a mixture of water and CH_3CN (5:1) giving Compound 9.

To a solution of Compound 9 (1.8 g) in THF (16 mL) and acetic acid (1.25 mL) is added tetra-n-butyl ammonium fluoride (6.1 mL of a 1M soluti n in THF), under N_2. The mixture is stirred at ambient temperature overnight and, upon

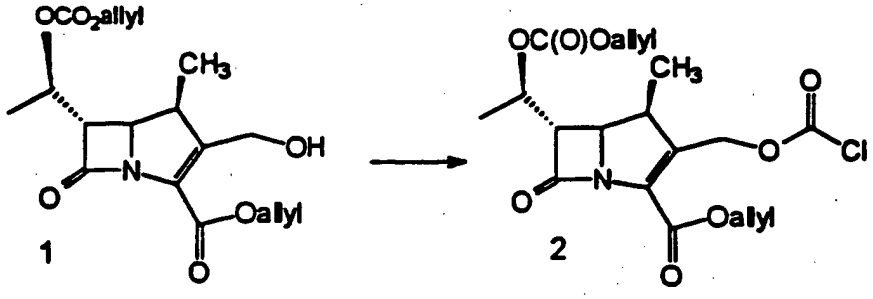
completion, is diluted with ether (25 mL). The solution is stirred for a half-hour, allowing the product to crystallize. The slurry is filtered through troyfelt and the solid residue is washed with ether to obtain Compound 10.

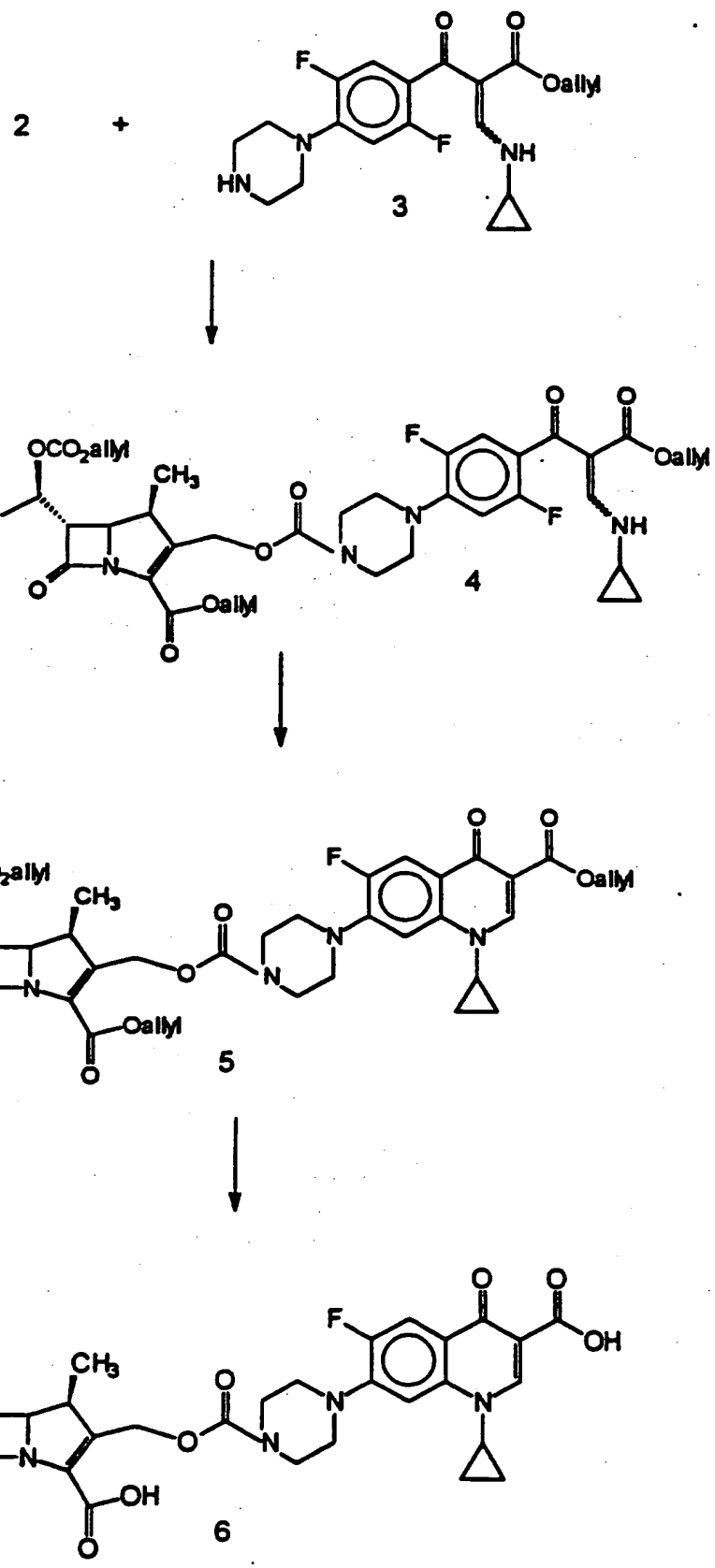
To a solution of Compound 10 (1.4 g) in CH_2Cl_2 (85 mL) is added tetrakis(triphenyl-phosphine)palladium (0) (240 mg), under N_2. The mixture is cooled (-10 to -5°C) and a cooled solution (<-10°C) of sodium ethylhexanoate (660 mg) in THF (42 mL) is added dropwise. The mixture is stirred for approximately 30 minutes, whereupon the resulting slurry is filtered and washed successively with CH_2Cl_2 and acetone, to obtain Compound 11.

To a solution of Compound 11 (0.9 g) in absolute ethanol (126 mL) is added highly acidic ion-exchange resin (1.8g, Amberlite IR-120 - plus), under N_2. The mixture is stirred at ambient temperature for approximately 5 hours, whereupon it is filtered through a sintered glass filtration funnel to remove the resin. The filtrate is reduced in vacuo to approximately one third of its volume, whereupon water (45 mL) is added. The mixture is strirred for a few minutes and then filtered. The solid obtained is washed with water and dried in vacuo overnight to obtain [5R-[5α,6α(R*)]]-3-[[[4-(3-Carboxy-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-quinolinyl)-1-piperazinyl]carbonyloxy]methyl]-6-(1-hydroxyethyl)-7-oxo-4-thia-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid (Compound 12).

EXAMPLE 3

Synthesis of [4R-[4α,5β,6β(R*)]]-3-[[[4-(3-Carboxy-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-quinolinyl)-1-piperazinyl]carbonyloxy]methyl]-6-(1-hydroxyethyl)-7-oxo-4-thia-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic Acid, Disodium salt.





Compound 3 (1.2 g), prepared in the same manner as Compound 5 in Example 11, is dissolved in CH_2Cl_2 (30 mL) and dried, under N_2, with activated molecular sieves. The solution is transferred to a second vessel, under N_2, and cooled (-15°C). N,O-bis(trimethylsilyl)acetamide (1.5 mL) is added and the mixture is allowed to stir for 15 minutes under N_2.

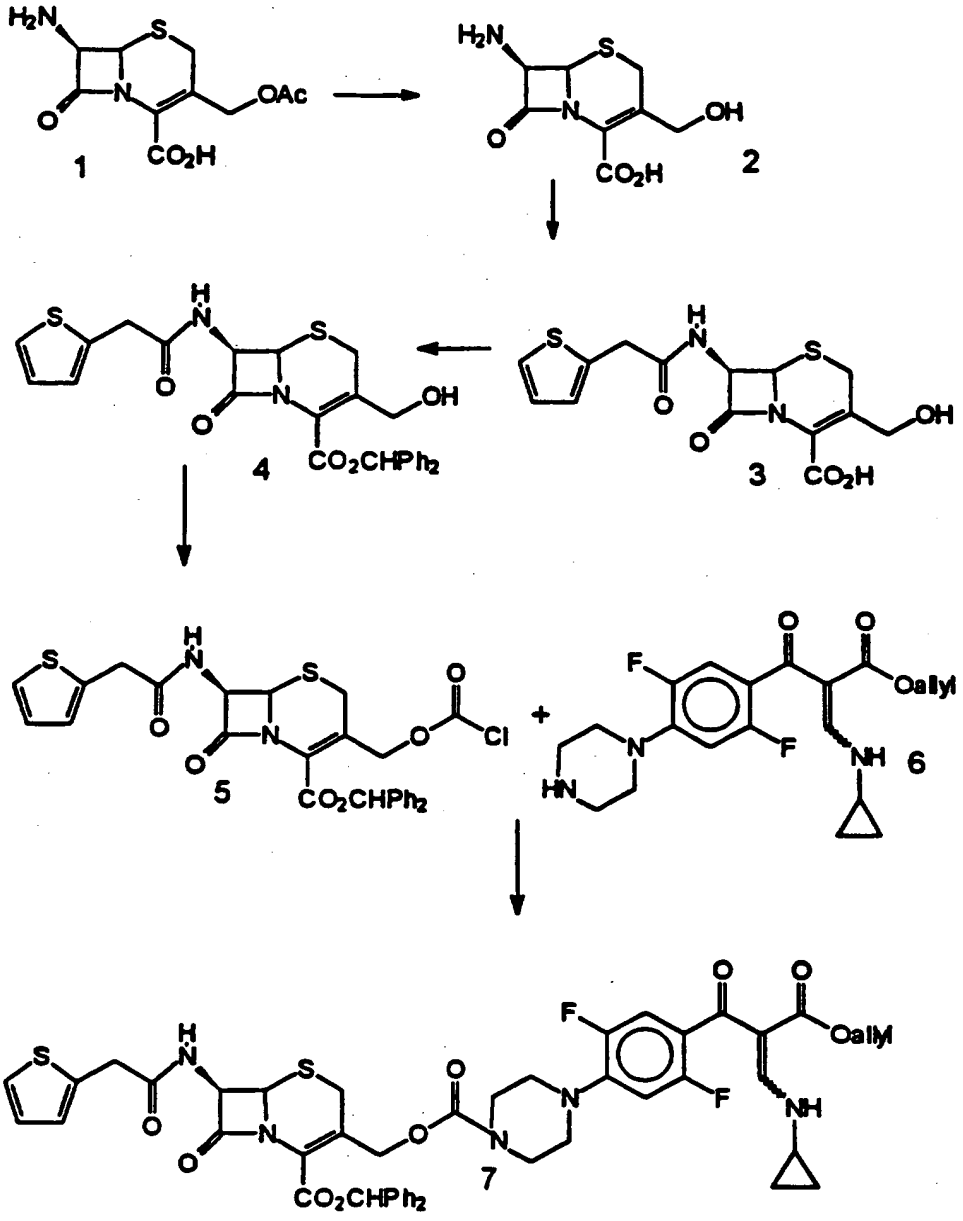
In a third vessel, Compound 1 (1.12 g), prepared according to Schmitt et al., 41 J. Antibiot. 780-787 (1988) (incorporated by reference herein), is dissolved in CH_2Cl_2 (30 mL) and dried, under N_2, with activated molecular sieves. The solution is transferred, under N_2, to a fourth vessel and N,N-diisopropylethylamine (0.58 mL) is added. The solution is stirred for 15 minutes at ambient temperature, under N_2, and cooled to -78°C. In a fifth vessel, to cooled (-78°C) CH_2Cl_2 (25 mL) is added 20% phosgene in toluene (1.86 mL) under N_2. The forementioned solution of Compound 1 is added dropwise while maintaining the solution temperature at less than -60°C. The reaction is stirred for 15 minutes and warmed to -15°C to provide Compound 2 which is then reacted *in situ* by dropwise addition of the forementioned solution of Compound 3, while maintaining the temperature below -15°C. The reaction is stirred at -15°C under N_2 until complete. The reaction mixture is quenched with water (90 mL), warmed to 0°C and stirred 10 minutes. The organic portion is separated and dried with (Na_2SO_4). The volatiles are evaporated *in vacuo* and the residue is subjected to column chromatography (silica) to give Compound 4.

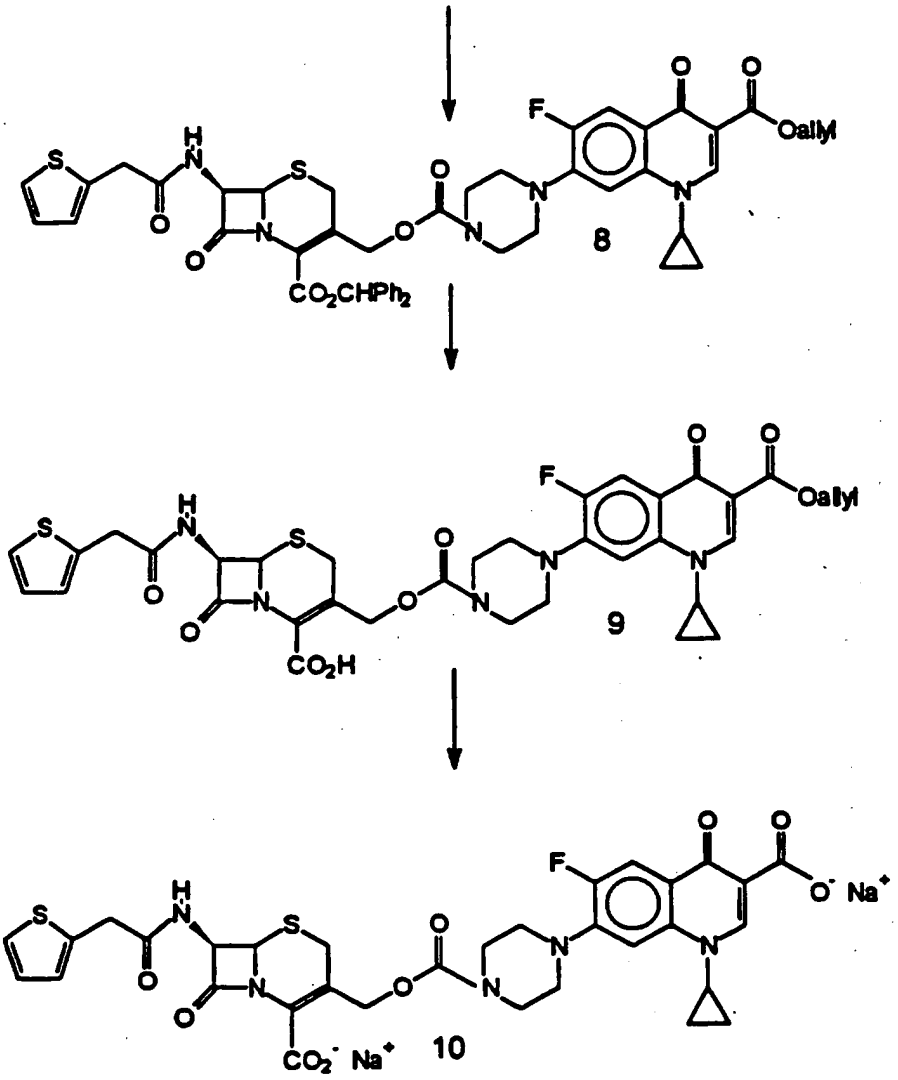
To a solution of Compound 4 (2.15 g) in CH_3CN (40 mL) is added N,O-bis(trimethylsilyl)acetamide (2.04 mL). The reaction mixture is stirred under N_2 at ambient temperature until complete. The reaction is quenched with water (10 mL), and the resulting slurry is filtered and washed with a mixture of water and CH_3CN (5:1) giving Compound 5.

To a cooled (0°C) solution of Compound 5 (1.9 g) in CH_2Cl_2 (75 mL) is added bis(triphenylphosphine)palladium-dichloride (78 mg), followed by water (3.5 mL). To this solution is added tributyltin hydride (4 mL) in one portion. The mixture is stirred at 0°C for 2 hours, whereupon sodium ethylhexanoate (715 mg) is added. The mixture is stirred for 20 minutes and the precipitate is partitioned between CH_2Cl_2 (350 mL) and water (450 mL). The aqueous phase is separated and lyophilized to provide a crude residue which is triturated with acetone (450 mL) to provide a solid that is subjected to column chromatography (reverse-phase silica) to provide [4R-[4α,5β,6β(R*)]]-3-[[[4-(3-Carboxy-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-quinolinyl)-1-piperazinyl] carbonyloxy]-methyl]-6-(1-hydroxy-ethyl)-7-oxo-4-thia-1-azabi-cyclo[3.2.0]hept-2-ene-2-carboxylic Acid, Disodium salt (Compound 6).

EXAMPLE 4

Synthesis of [6R-[6α,7β]]-3-[[[4-(3-Carboxy-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-quinolinyl)-1-piperazinyl]carbonyloxy]methyl]-8-oxo-7-[(2-thienylacetyl)amino]-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic Acid, Disodium Salt.





To a cooled (-5°C) suspension of 7-aminocephalosporanic acid (20 g) (Compound 1) in methanol (38 mL) is added 1N NaOH (73.5 mL) over 30 minutes. Additional 1N NaOH (73.5 mL) is then added over 7 minutes at 2-5°C to provide Compound 2. Compound 2 is further reacted in situ by addition of acetone (50 mL) and $NaHCO_3$ (18.51 g) followed by dropwise addition of 2-thiopheneacetyl chloride (9 mL) over 30 minutes at 0-5°C, while maintaining a pH of 7 by simultaneous addition of $NaHCO_3$. The solution is washed with EtOAc (100 mL) and the layers are separated. The aqueous phase is layered with EtOAc (160 mL) and the resulting mixture is acidified at 0°C with concentrated HCl. The layers are separated and the aqueous phase is extracted with EtOAc (160 mL). The combined EtOAc layers are filtered and the volatiles removed in vacuo to near dryness. The precipitate that results is filtered and dried in in vacuo to provide Compound 3.

T a solution of benzophenone hydrazone (10 g) in CH_2Cl_2 (51 mL) is added a 1% w/v solution of iodine in CH_2Cl_2 (2.05 mL) and 1,1,3,3-tetramethylguanidine (6.43 g). 3-Chloroperoxybenzoic acid (9.7 g) is then added in small portions at room temperature. The solvent is removed in vacuo to provide diphenyl diazomethane. A solution of diphen· diazomethane (8.78 g) in EtOAc (19 mL) is then added to a cooled (5°C) solution of Compound 3 in THF (150 mL) and EtOAc (150 mL). The mixture is stirred until completion whereupon it is evaporated to dryness in vacuo. THF (64 mL) is added and the insolubles are filtered off. The filtrate is evaporated in vacuo until crystals begin to form. EtOAc (64 mL) is then added and the mixture is stirred for 1.5 hours at 0-5°C. The resulting solid is filtered to provide Compound 4.

Compound 6 (1.9 g), prepared in the same manner as Compound 5 in Example 2, is dissolved in CH_2Cl_2 (58 mL) and activated 4A molecular sieves (500 mg) are added under N_2. After stirring for 30 minutes at room temperature, the solution is transferred via canula to a second vessel. The solution is cooled (-15°C) and N,O-bis(trimethylsilyl)acetamide (2.37 mL) is added under N_2. The mixture is allowed to stir for 15 minutes under N_2. Concurrent with this procedure, t a cooled (0°C) solution of Compound 4 (2.52 g) in CH_2Cl_2 (48 mL) in a third vessel is added activated 4A molecular sieves (500 mg), under N_2. After stirring for 30 minutes, the solution is transferred via canula to a fourth vessel and N,N-diisopropylethylamine (0.93 mL) is added under N_2. The solution is stirred for 15 minutes at 0°C and cooled to -78°C. In a fifth vessel, to cooled (- 78°C) CH_2Cl_2 (40 mL) is added 20% phosgene in toluene (3 mL) under N_2. The forementioned solution of Compound 4 is added dropwise while maintaining the solution temperature at less than -60°C. The reaction is stirred for 15 minutes and warmed to -15°C to provide Compound 5 which is then reacted in situ by dropwise addition of the forementioned solution of Compound 6, while maintaining the temperature below -15°C. The reaction is stirred at -15°C under N_2 until complete. The reaction mixture is quenched with water (30 mL), warmed to 0°C and stirred 10 minutes. The organic portion is separated and dried with (Na_2SO_4). The volatiles are evaporated in vacuo and the residue is subjected to column chromatography (silica) to give Compound 7.

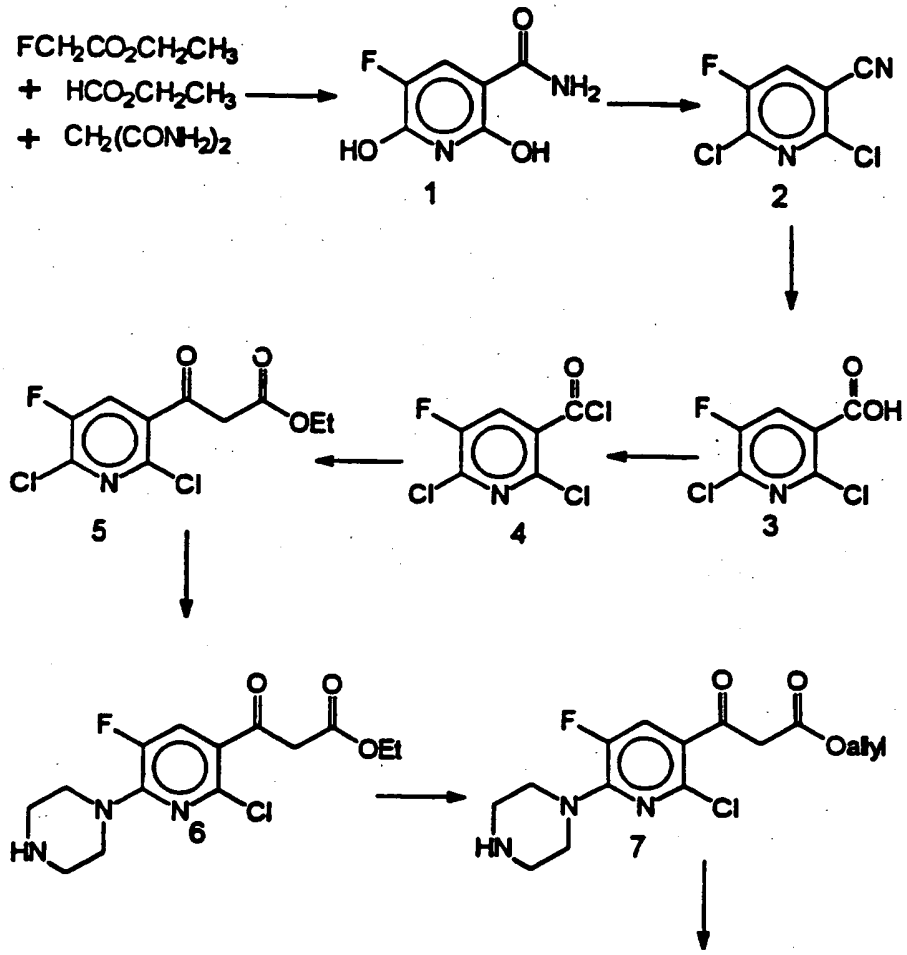
To a solution of Compound 7 (2.9 g) in CH_3CN (55 mL) is added N,O-bis(trimethylsilyl)acetamide (2.27 mL). The reaction mixture is stirred under N_2 at ambient temperature until complete. The reaction is quenched with water (55 mL), and the resulting slurry is filtered and washed with a mixture f water and CH_3CN (5:1) giving Compound 8.

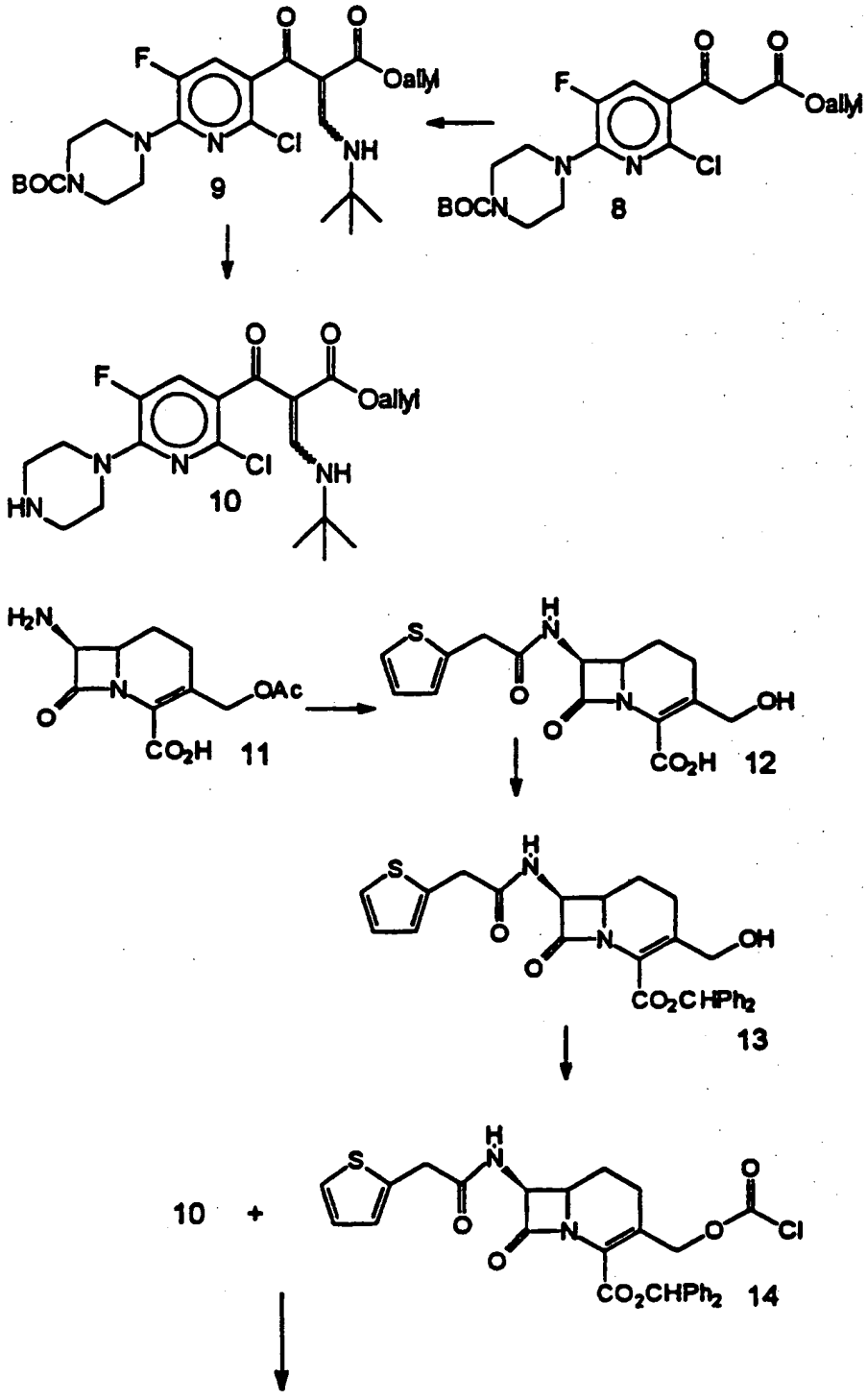
To a cooled (-15°C) solution of Compound 8 (2.2 g) in anhydrous anisole (22 mL) is added TFA (22 mL), dropwise. The cooling bath is removed and the mixture is stirred for 30 minutes. The volatiles are removed in vacuo and ether (75 mL) is added to the residue. The mixture is stirred under N_2 for 30 minutes and the resulting solid is filtered to obtain Compound 9.

To a solution of Compound 9 (1.6 g) in CH_2Cl_2 (90 mL) is added tetrakis(triphenylphosphine)palladium (0) (246 mg), under N_2. The mixture is cooled (-10 to -5°C) and a cooled solution (<-10°C) of sodium ethylhexanoate (708 mg) in THF (45 mL) is added dropwise. The mixture is stirred for approximately 30 minutes, whereupon the resulting slurry is filtered and washed successively with CH_2Cl_2 and acetone, to provide [6R-[6α,7β]]-3-[[[4-(3-Carboxy-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-quinolinyl)-1-piperazinyl]-carbonyloxy]methyl]-8-oxo-7-[(2-thienylacetyl)amino]-5-thia-1-azabicyclo[4.2.0]-oct-2-ene-2-carboxylic Acid, Disodium Salt (Compound 10).

Example 5

Synthesis of [6R-[6α,7β]]-3-[[[4-[3-Carboxy-1-(1,1-dimethylethyl)-6-fluoro-1,4-dihydro-4-oxo-1,8-napthyridin-7-yl]-1-piperazinyl]carbonyloxy]-methyl]-8-oxo-7-[(2-thienylacetyl)amino]-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic Acid, Disodium Salt.

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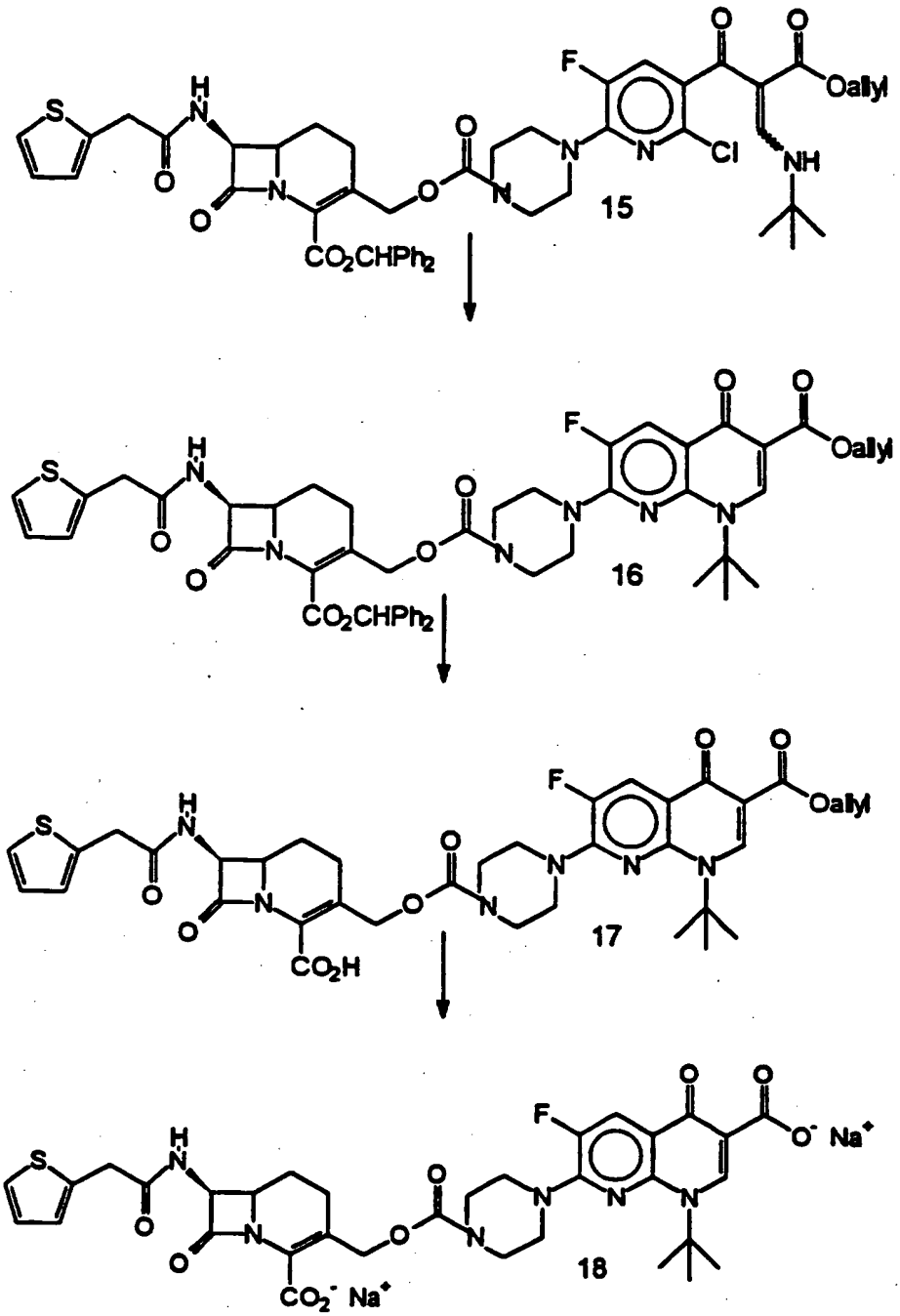


Solid sodium ethoxide (424.5 g) is added in portions (20 min) via a Gooch tube to a vigorously stirred, cold (ice bath) solution of ethyl fluoroacetate (450 g) and ethyl formate (525 g) under argon. The ice bath is rem ved and the reacti n mixture is stirred for 3.5 h at room temperature. Malondiamide (745.5 g) is added in portions over 10 min with the aid of 5.4 L of absolute EtOH t wash in the solid. The mixture is slowly heated to reflux where upon the mixture becomes a thick

paste. The reacti n mixture is cooled in an ice bath and water (4.23 L) is added over 10 min. followed by addition of conc. HCl (843 mL), while stirring and cooling. The mixture is filtered and the solid is washed successively with H_2O and EtOH to give Compound 1.

In an argon purged 5-L 3-neck flask is added Compound 1 (300 g) and phosphorus pentachloride (1200 g). The mixture is stirred thoroughly and is slowly heated to 110°C and maintained at 110°C for about 1 h. The mixture is distilled under partial vacuum to remove $POCl_3$. The concentrated residue is mixed with cold water (3L) and stirred. The mixture is filtered and the solid is washed successively with H_2O (2 x 1L) and isopropyl alcohol-H_2O (1:1) to give, after vacuum drying, Compound 2.

A solution of Compound 2 (200 g) in concentrated sulfuric acid (1.35 L) is heated at 90°C for 1.5 h. The solution is cooled to about 60°C and H_2O (2.67 L) is slowly added while maintaining the temperature below 95°C. The reaction mixture is heated at 100°C for 3 h and then stored overnight at 5C°. The mixture is filtered, and the solid is air dried to give crude Compound 3. Compound 3 is purified by mixing with 5 L of EtOAc and adding decolorizing carbon (100 g). The mixture is filtered, and the filtrate is concentrated in vacuo to 3 L. The solution is diluted with hexanes (7 L) and further evaporated to 2 L. An additional 4 L of hexanes is added. The solid is collected and washed with hexanes (1 L) to give Compound 3.

A mixture of Compound 3 (140 g) and thionyl chloride (250 mL) is stirred and heated at reflux for 2 h. The solution is cooled and evaporated in vacuo. The residue is evaporated further with toluene (3 x 600 mL, freshly filtered through anhydrous Na_2SO_4) to give the crude Compound 4, which is used immediately in the subsequent step.

A 2.5M solution of n-butyl lithium (1270 mL) in hexanes is added over 2.5 h to a stirred solution of ethyl hydrogen malonate (197.1 g) in THF (3.4 L) at -50 to -65°C under an Ar atmosphere. The cooling bath is replaced with warm water to bring the temperature to -5°C. The pasty mixture is recooled in the dry ice-acetone bath, and the crude Compound 4 in THF (250 mL) is added dropwise (1.5 h) while keeping the temperature below -50°C. After the addition is complete, the cooling bath is removed, and the reaction mixture is left to warm to room temperature overnight. The mixture is poured in about 4 equal portions to a rapidly stirred solution of conc. HCl (270 mL) and H_2O (2.5 L). The mixture is stirred for about 30 min and the temperature rises to 34°C. The layers are separated, and the aqueous layer is extracted (by stirring) with EtOAc (2 x 2 L). The combined organic material is washed with saturated aqueous $NaHCO_3$ (1.8 L and 2 x 1 L).

These aqueous washes are back extracted with EtOAc (800 mL). The combined EtOAc solutions are dried over Na_2SO_4 then concentrated in vacuo to a residue. This material is chromatographed on a 1.4 kg silica gel column eluted with CH_2Cl_2. The fractions containing purified product are combined and concentrated in vacuo to give (after cold hexane trituration) Compound 5 as crystals.

To a solution of Compound 5 (18.0 g) in THF (360 mL) is added piperazine (22 g). The mixture is refluxed under N_2 until complete and the THF is removed under reduced pressure. The residue is slurried in EtOAc (175 mL), and the excess piperazine is filtered off and rinsed with EtOAc. The EtOAc filtrate is washed with water (2 x 175 mL) and the combined aqueous layers are extracted with EtOAc (100 mL). The combined EtOAc layers are dried ($MgSO_4$) and treated with activated charcoal. The solvents are evaporated in vacuo and the residue is crystallized from isopropyl ether to give Compound 6.

To a solution of allyl alcohol (84 g) in toluene (120 mL) is added 4-dimethylaminopyridine (2.2 g), under N_2. Compound 6 (20 g) is added and the mixture is heated to reflux. Upon completion, the reaction mixture is cooled and saturated ammonium chloride (300 mL) is added, followed by the additi n of EtOAc (350 mL). The layers are separated and the EtOAc portion is washed with water (4 x 100 mL) and brine (2 x 75 mL), and dried ($MgSO_4$). The solvents are removed in vacuo and the residue is subjected to column chromatography (silica) to provide Compound 7.

To a solution of Compound 7 (21 g) in $CHCl_3$ (400 mL) is added a soluti n of di-t-butylcarbonate (15 mL) in $CHCl_3$ (75 mL), under N_2. The reaction is stirred for 5 minutes under N_2 at ambient temperature and evaporated in vacuo. Hexanes are added to the residue to give Compound 8.

To a solution of Compound 8 (17.8 g) in triethylorthoformate (10.9 mL) is added acetic anhydride (34.8 mL). The mixture is fitted with a Dean-Stark trap and stirred at 130°C for 1.5 hours under N_2. The volatiles removed in vacuo and the residue is dissolved in CH_2Cl_2 (65 mL). The solution obtained is cooled to 0°C and tert-butylamine is added (5.8 mL). The reaction is stirred at 0°C for 5 minutes under N_2, allowed to warm to ambient temperature and stirred for 1 hour. The volatiles are removed in vacuo and the residue obtained is subjected to column chromatography (silica) to provide Compound 9.

To a cooled solution of Compound 9 (12 g) in anisole (90 mL) at 5-10°C is added TFA (90 mL). After stirring for 5 minutes under N_2, the ice bath is removed and the reaction is warmed t ambient temperature. After 2 hours, most f th TFA and some of the anisole is removed in vacuo. The residue is slurried in Et_2O (300

mL) and filtered. The solid is dissolved in a mixture of CH_2Cl_2 (100 mL) and saturated $NaHCO_3$ (100 mL) and stirred for 10 min. The CH_2Cl_2 portion is separated, dried ($MgSO_4$), treated with activated charcoal, and evaporated in vacuo. The residue is crystallized with hexane to give Compound 10.

To a cooled (-5°C) suspension of (±)-7β-amino-1-methylenedethiacephalosporanic acid (21.5 g) (Compound 11), prepared as described in R. Guthikonda et al., 96 J. Am. Chem. Soc. 7584 (1974), which is incorporated herein by reference, in methanol (44 mL) is added 1N NaOH (84.53 mL) over 30 minutes. Additional 1N NaOH (84.53 mL) is then added over 8 minutes at 2-5°C. Acetone (58 mL) and $NaHCO_3$ (21.29 g) are added, followed by dropwise addition of 2-thiopheneacetyl chloride (10.4 mL) over 30 minutes at 0-5°C, while maintaining a pH of 7 by simultaneous addition of $NaHCO_3$. The solution is washed with EtOAc (110 mL) and the layers are separated. The aqueous phase is layered with EtOAc (170 mL) and the resulting mixture is acidified at 0°C with concentrated HCl. The layers are separated and the aqueous phase is extracted with EtOAc (170 mL). The combined EtOAc layers are filtered and the volatiles removed in vacuo to near dryness. The precipitate that results is filtered and dried in in vacuo to provide Compound 12.

To a solution of benzophenone hydrazone (11.3 g) in CH_2Cl_2 (58 mL) is added a 1% w/v solution of iodine in CH_2Cl_2 (2.3 mL) and 1,1,3,3-tetramethylguanidine (7.29 g). 3-Chloroperoxybenzoic acid (11 g) is then added in small portions at room temperature. The solvent is removed in vacuo to provide diphenyl diazomethane. A solution of diphenyl diazomethane (10 g) in EtOAc (22 mL) is then added to a cooled (5°C) solution of Compound 12 (9.7 g) in THF (170 mL) and EtOAc (170 mL). The mixture is stirred until completion whereupon it is evaporated to dryness in vacuo. THF (73 mL) is added and the insolubles are filtered off. The filtrate is evaporated in vacuo until crystals begin to form. EtOAc (73 mL) is then added and the mixture is stirred for 1.5 hours at 0-5°C. The resulting solid is filtered to provide Compound 13.

Compound 10 (7.1 g) is dissolved in CH_2Cl_2 (160 mL) and activated 4A molecular sieves (1.5 g) are added under N_2. After stirring for 30 minutes at room temperature, the solution is transferred via canula to a second vessel. The solution is cooled (-15°C) and N,O-bis(trimethylsilyl)acetamide (8.17 mL) is added under N_2. The mixture is allowed to stir for 15 minutes under N_2. Concurrent with this procedure, Compound 13 (9.1 g) is dissolved in CH_2Cl_2 (160 mL) in a third vessel and activated 4A molecular sieves (1.5 g) are added, under N_2. After stirring f r 30 minutes, th solution is transferred via canula to a fourth vessel and N,N-

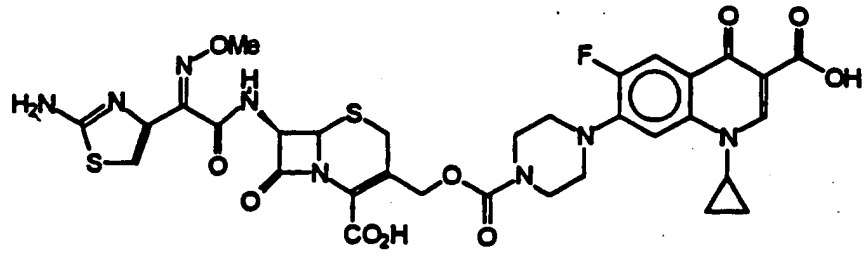
diisopropylethylamine (3.21 mL) is added under N_2. The solution is stirred for 15 minutes at ambient temperature and cooled to -78°C. In a fifth vessel, t cooled (-78°C) CH_2Cl_2 (150 mL) is added 20% phosgene in toluene (10.4 mL) under N_2. The forementioned solution of Compound 13 is added dropwise while maintaining the solution temperature at less than -60°C. The reaction is stirred for 15 minutes and warmed to -15°C to provide Compound 14, which is then reacted in situ by dropwise addition of the forementioned solution of Compound 10, while maintaining the temperature below -15°C. The reaction is stirred at -15°C under N_2 until complete. The reaction mixture is quenched with water (150 mL), warmed to 0°C and stirred 10 minutes. The organic portion is separated and dried (Na_2SO_4). The volatiles are evaporated in vacuo and the residue is subjected t column chromatography (silica) to give Compound 15.

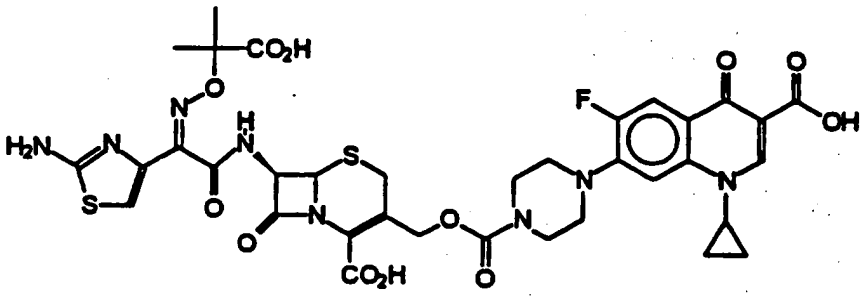
To a solution of Compound 15 (12.1 g) in CH_3CN (140 mL) is added N,O-bis(trimethylsilyl)acetamide (9 mL). The reaction mixture is stirred under N_2 at ambient temperature until complete. The reaction is quenched with water (140 mL), and the resulting slurry is filtered and washed with a mixture of water and CH_3CN (5:1) giving Compound 16.

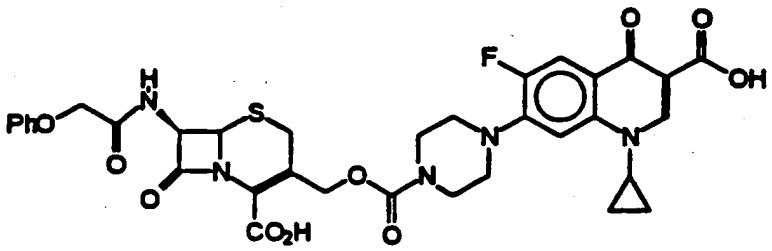
To a cooled (-15°C) solution of Compound 16 (8.6 g) in anhydrous anisole (80 mL) is added TFA (80 mL), dropwise. The cooling bath is removed and the mixture is stirred for 30 minutes. The volatiles are removed in vacuo and ether (200 mL) is added to the residue. The mixture is stirred under N_2 for 30 minutes and the resulting solid is filtered to obtain Compound 17.

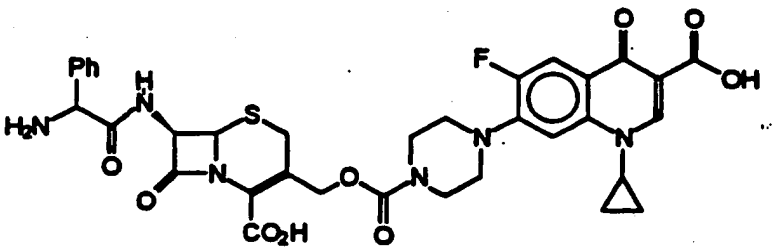
To a solution of Compound 17 (6.4 g) in CH_2Cl_2 (340 mL) is added tetrakis(triphenylphosphine)palladium (0) (932 mg), under N_2. The mixture is cooled (-10 to -5°C) and a cooled solution (<-10°C) of sodium ethylhexanoate (2.68 g) in THF (170 mL) is added dropwise. The mixture is stirred for approximately 30 minutes, whereupon the resulting slurry is filtered and washed successively with CH_2Cl_2 and acetone to provide [6R-[6α,7β]]-3-[[[4-[3-Carboxy-1-(1,1-dimethylethyl)-6-fluoro-1,4-dihydro-4-oxo-1,8-napthyridin-7-yl]-1-piperazinyl]carbonyloxy]methyl]-8-oxo-7-[(2-thienylacetyl)amino]-1-azabicyclo-[4.2.0]oct-2-ene-2-carboxylic Acid, Disodium Salt (Compound 18).

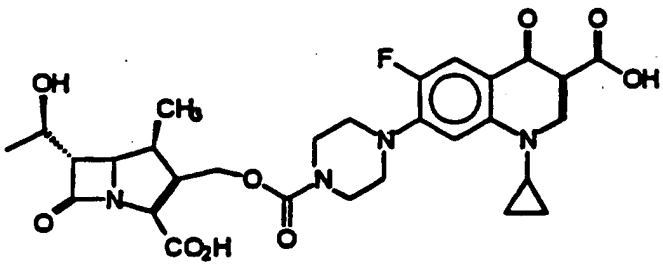
The following compounds are prepared according to Examples 1 thr ugh 5, with substantially similar results.

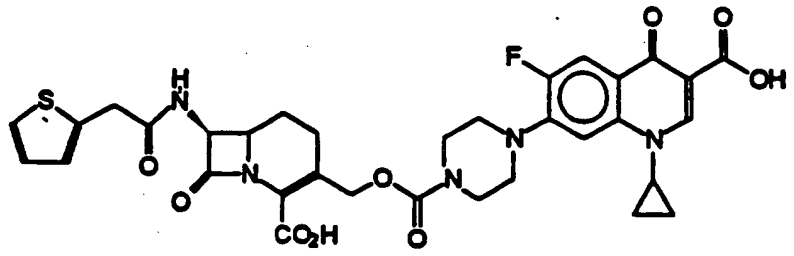


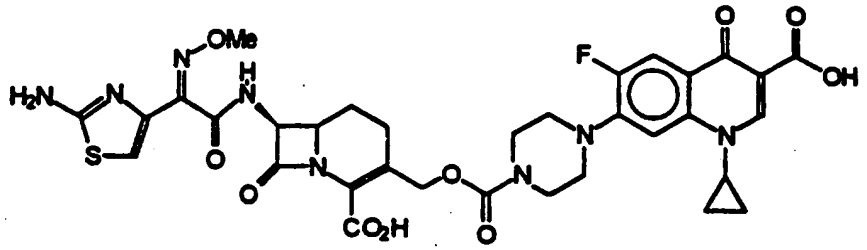


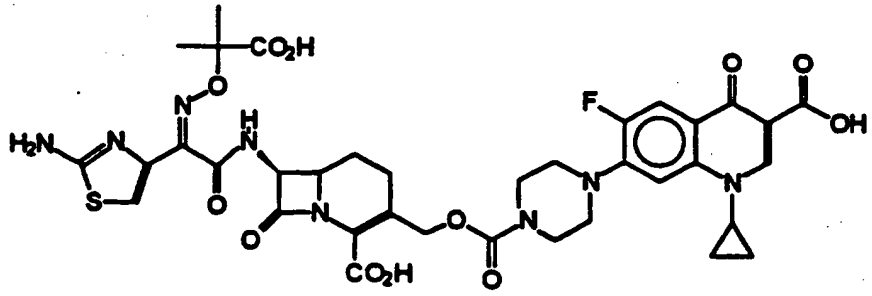


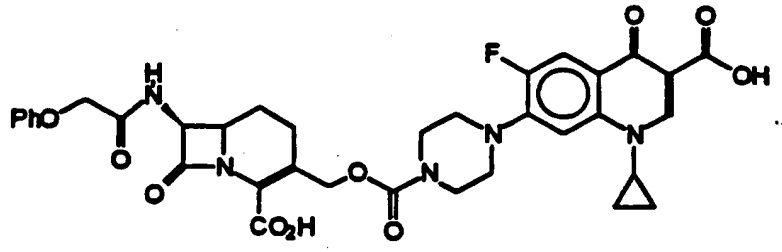


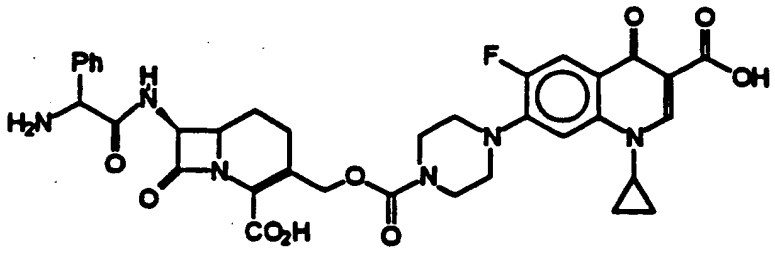


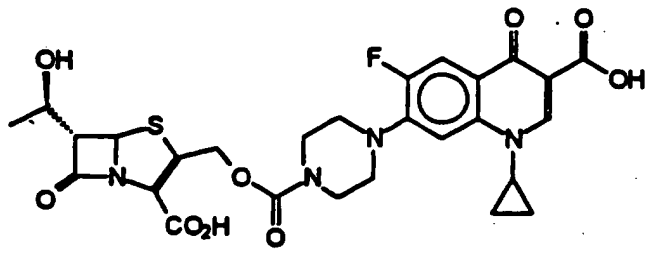


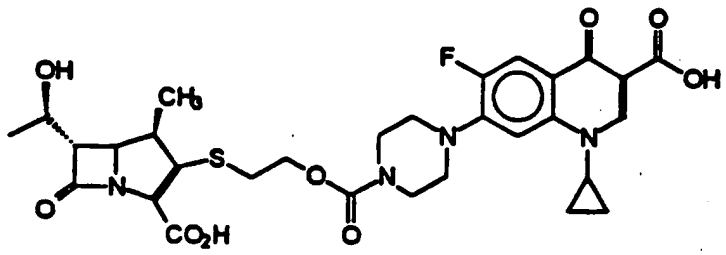


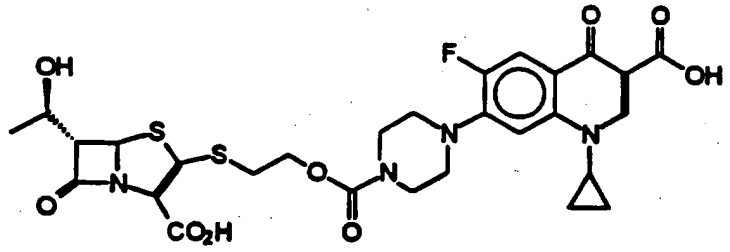


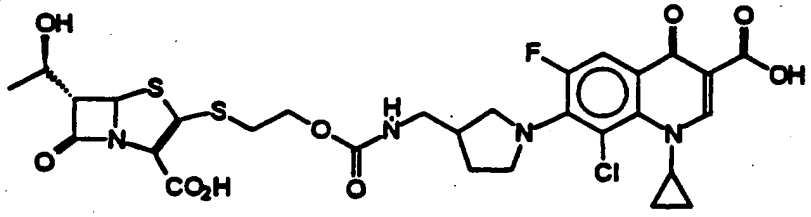


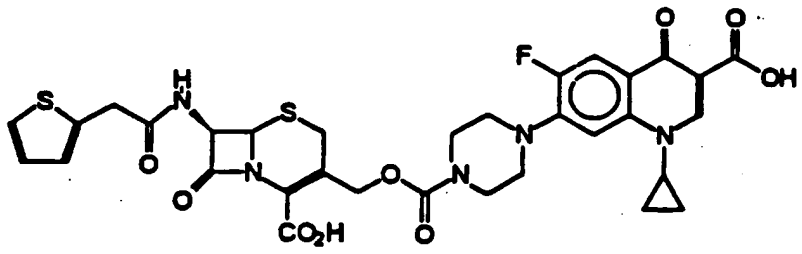


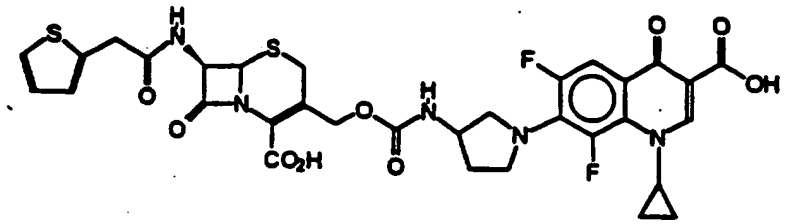


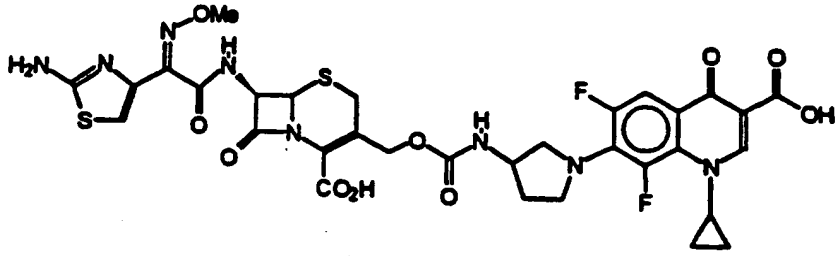


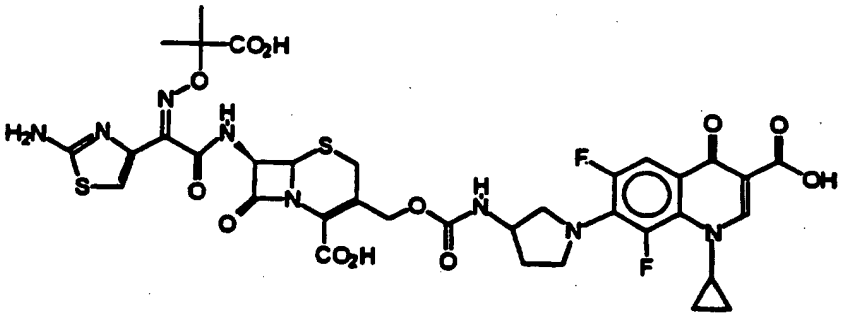


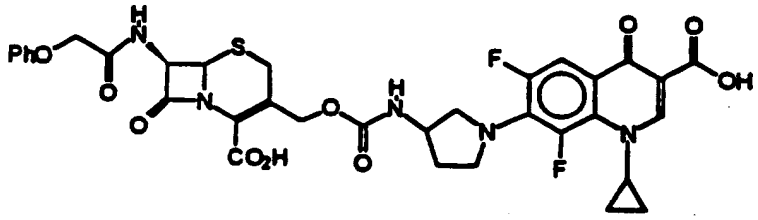


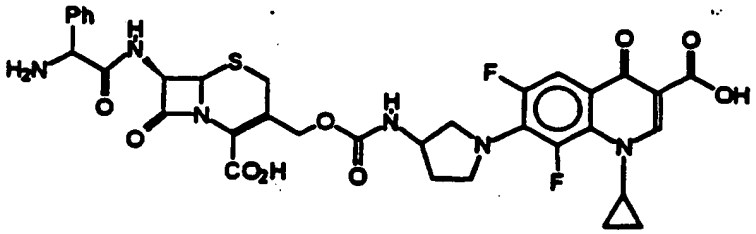


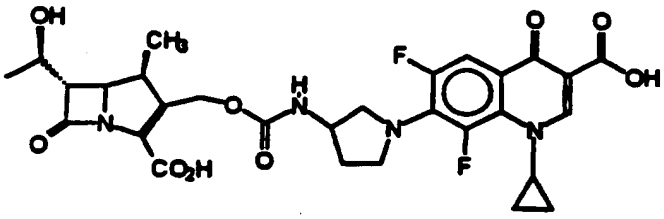


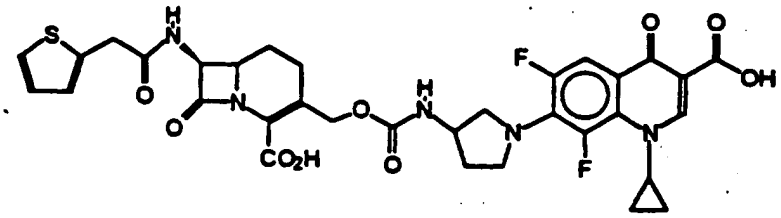


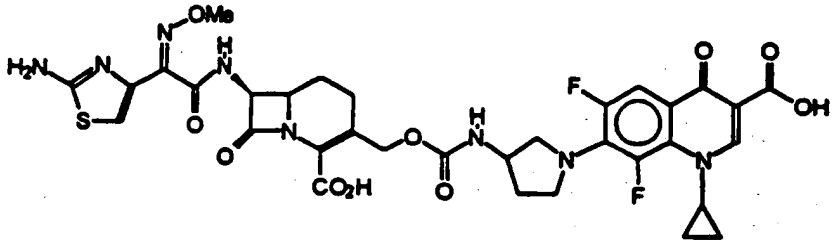


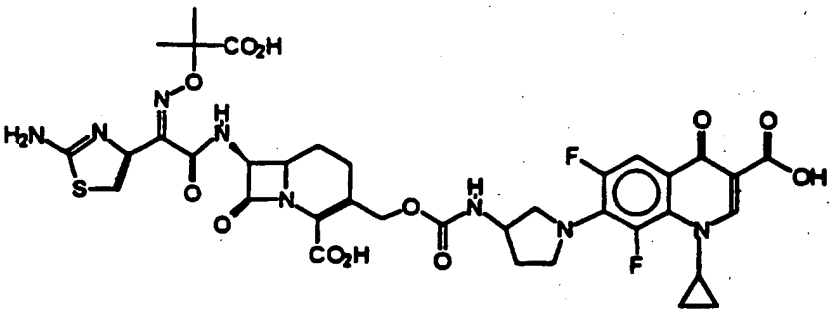


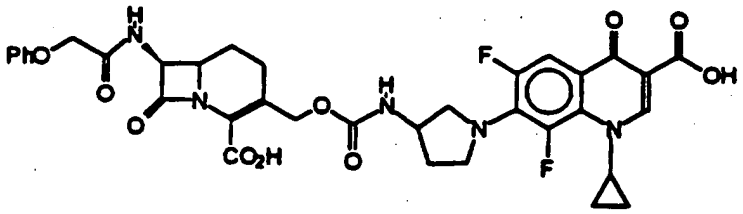


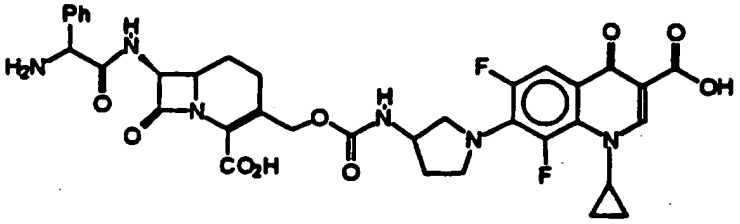


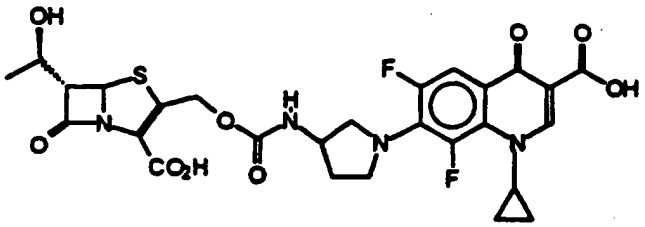












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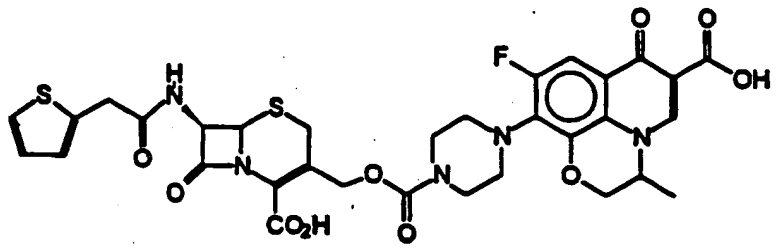
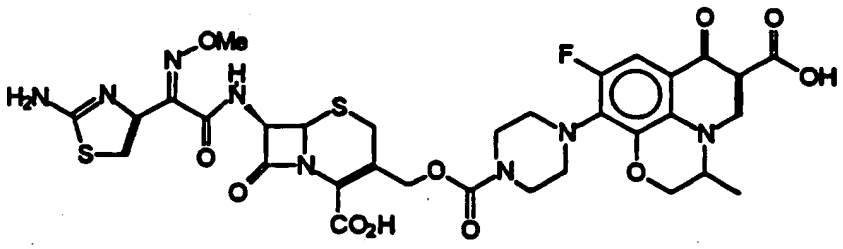
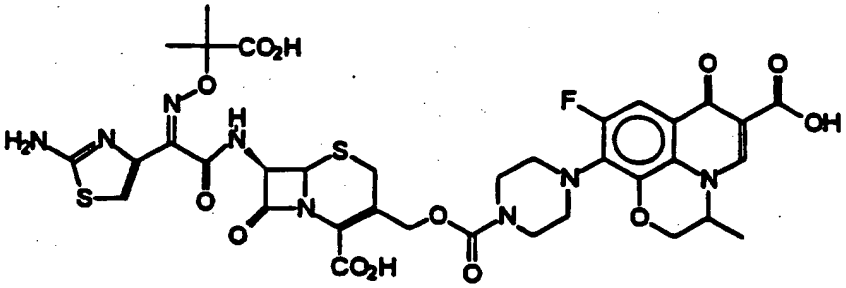
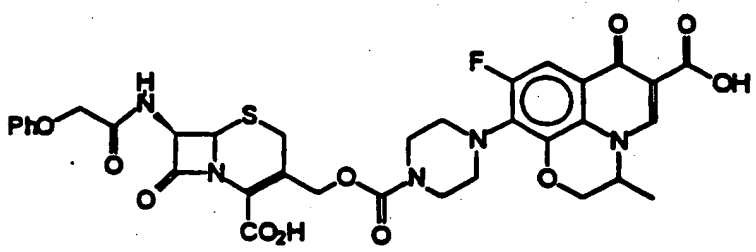
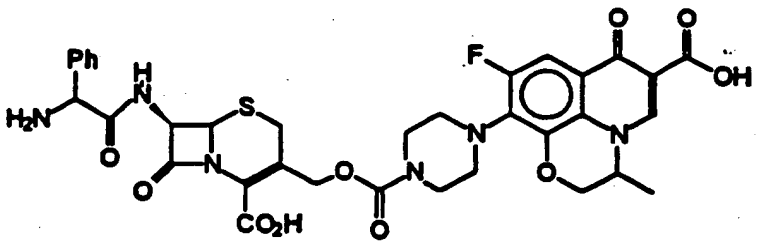
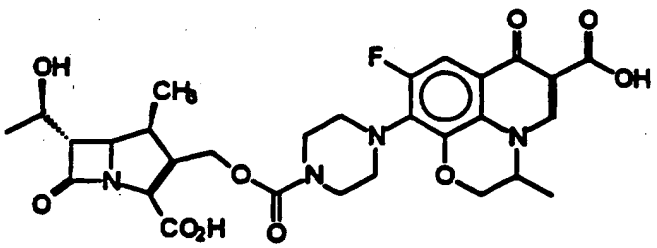


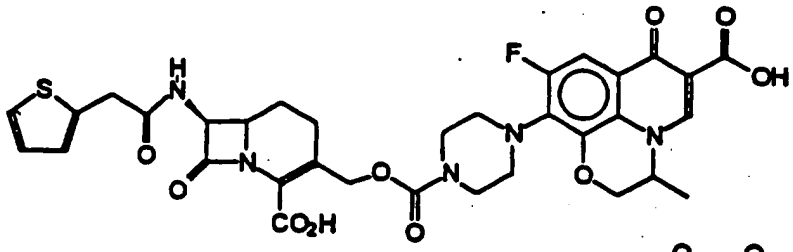


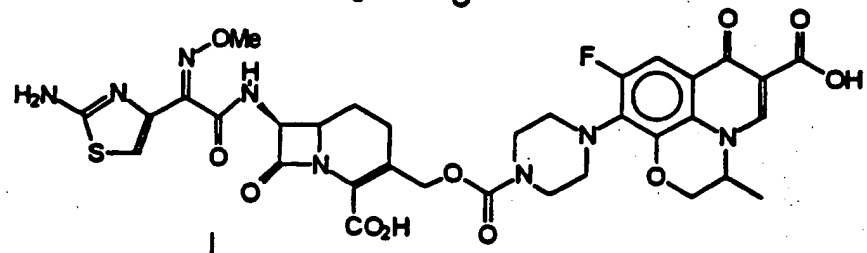


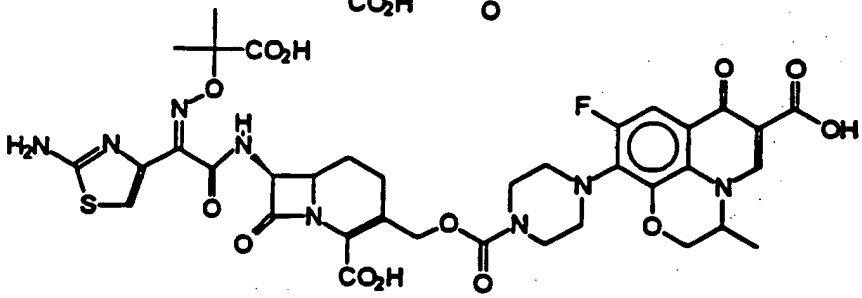


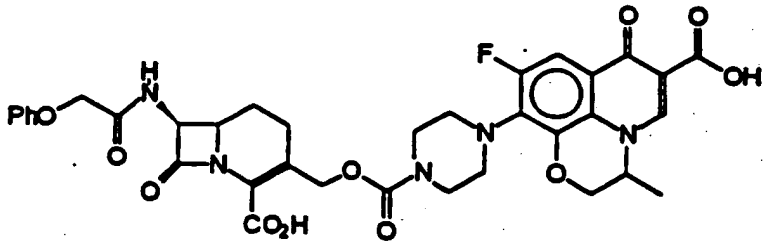


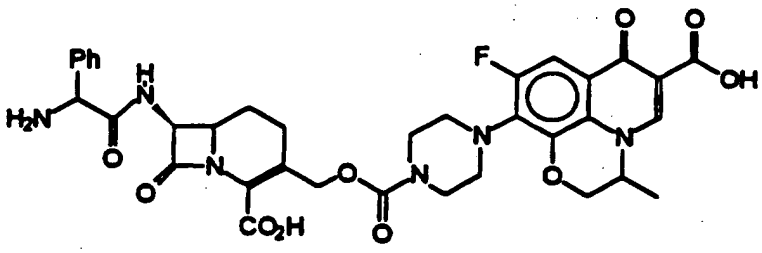


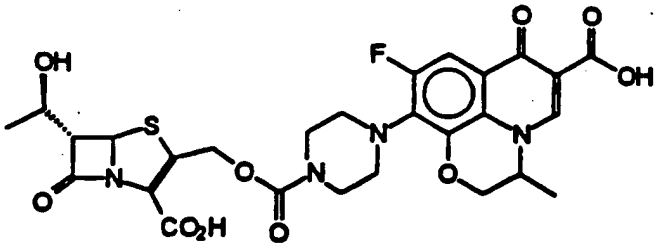


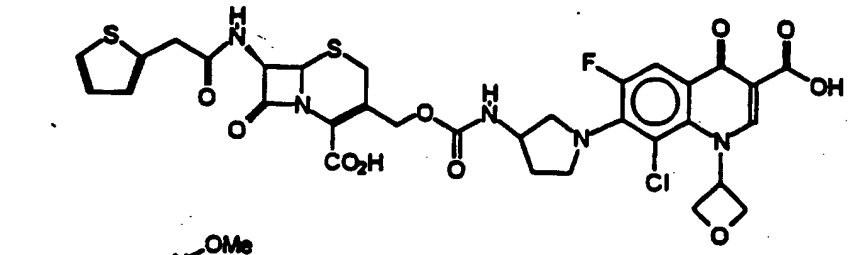


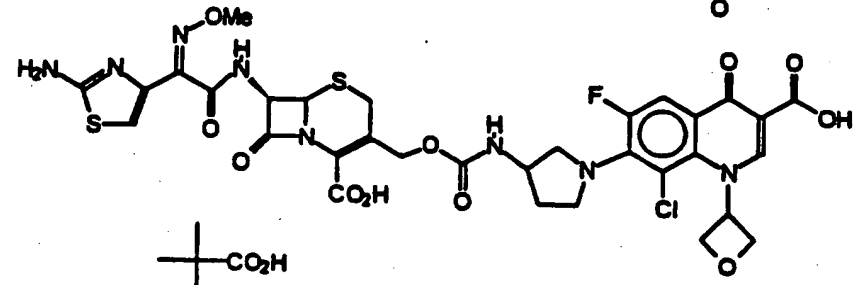


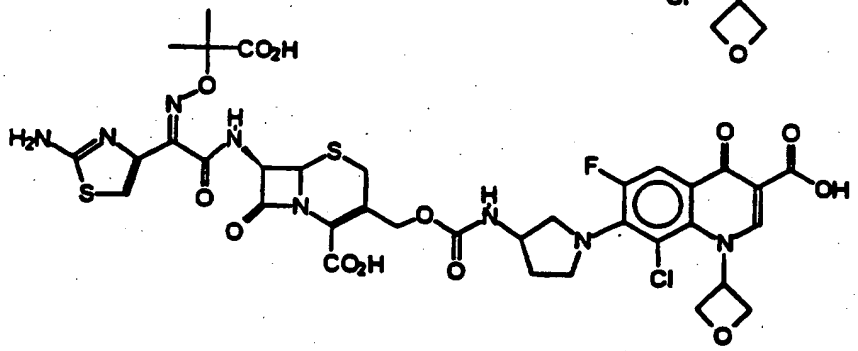


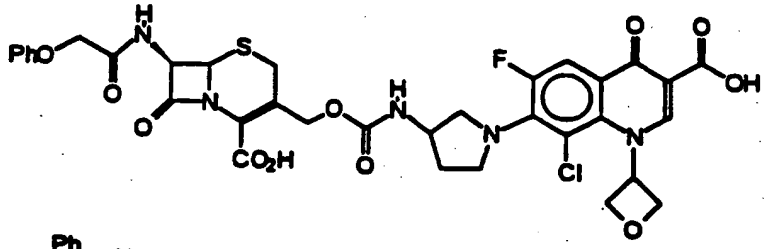


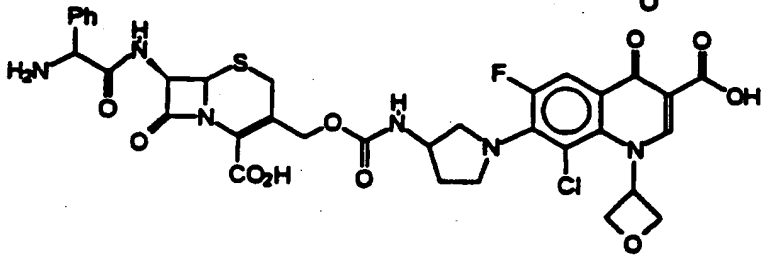


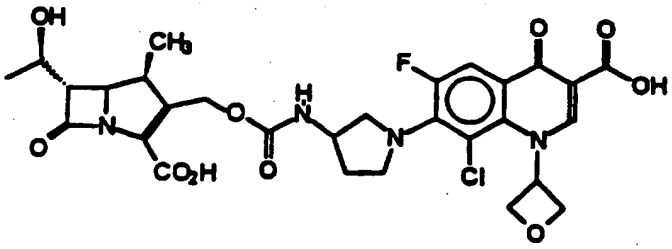


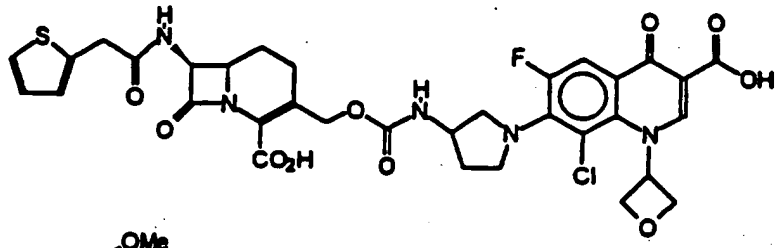


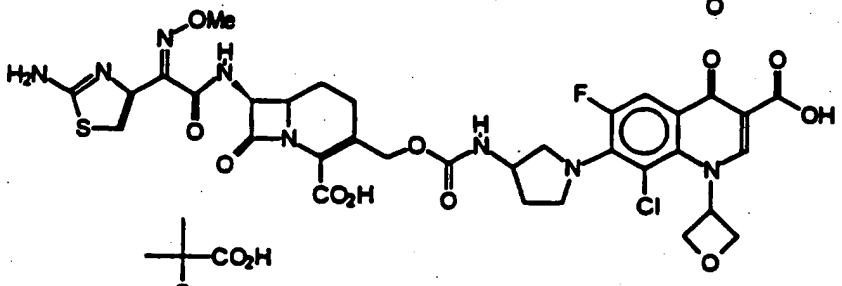


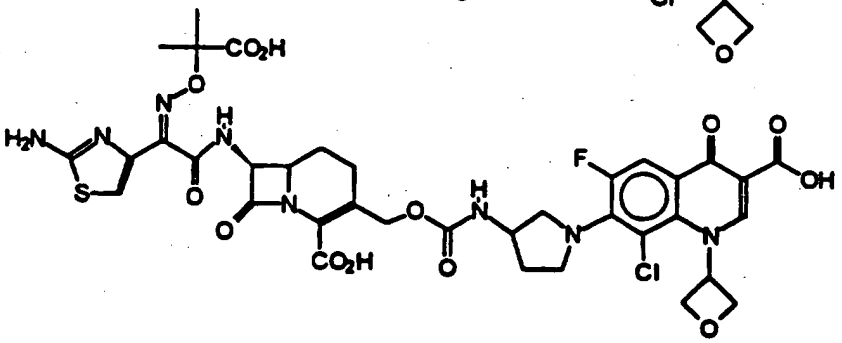


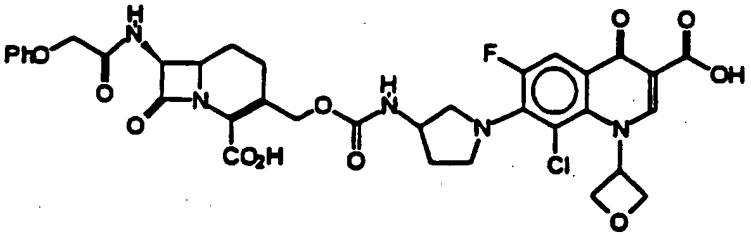


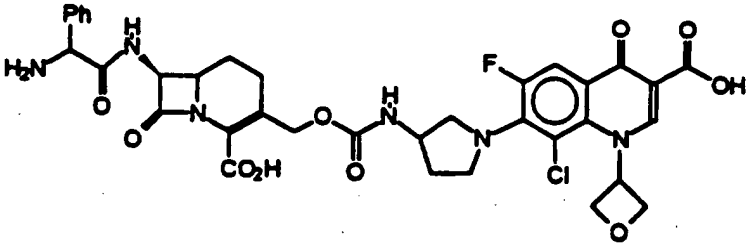


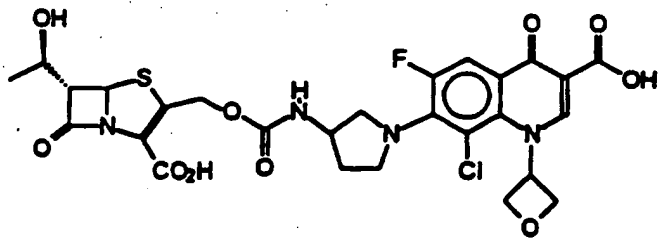


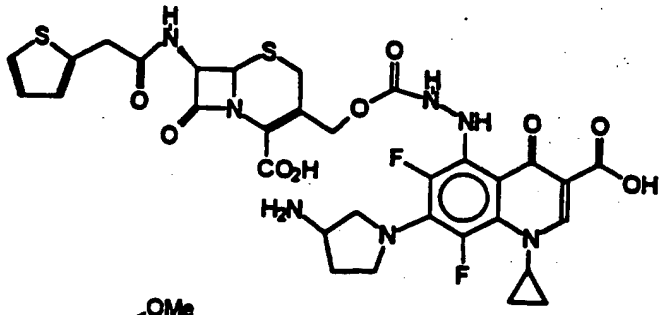


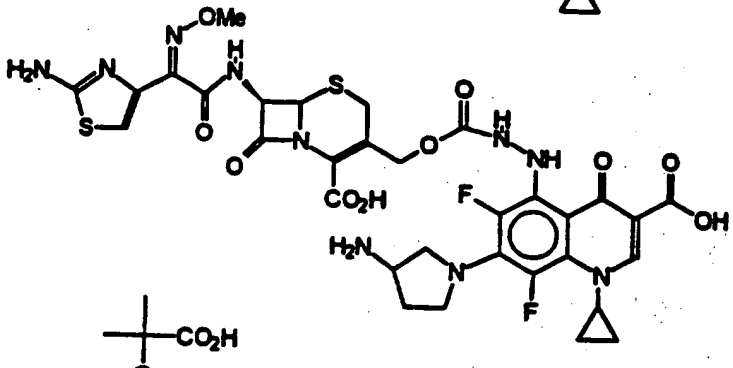


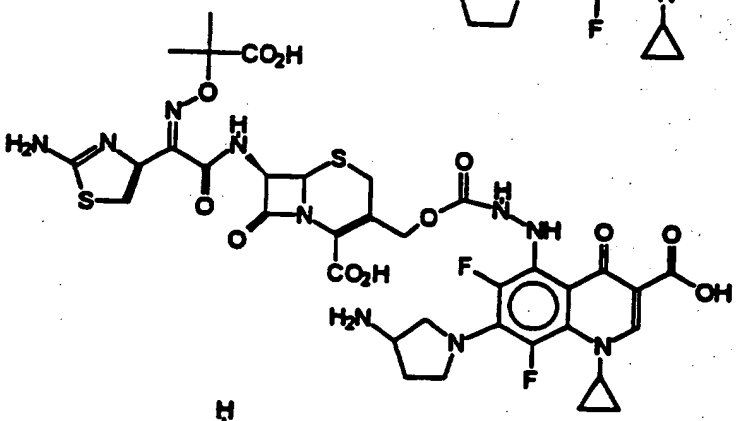


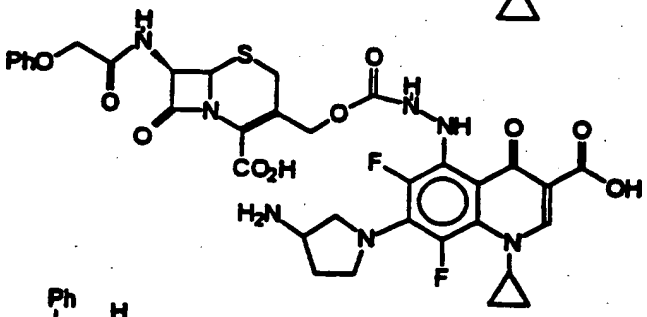


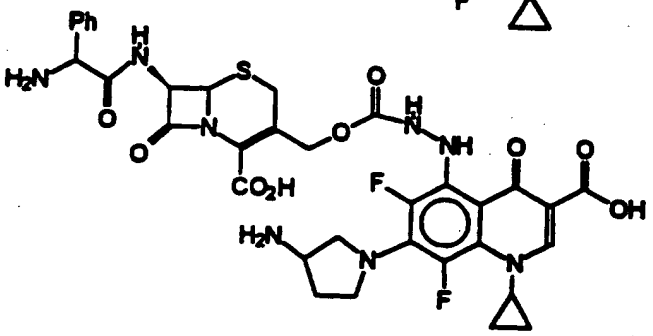


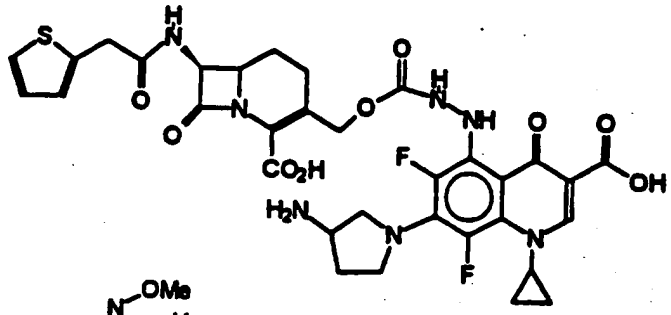


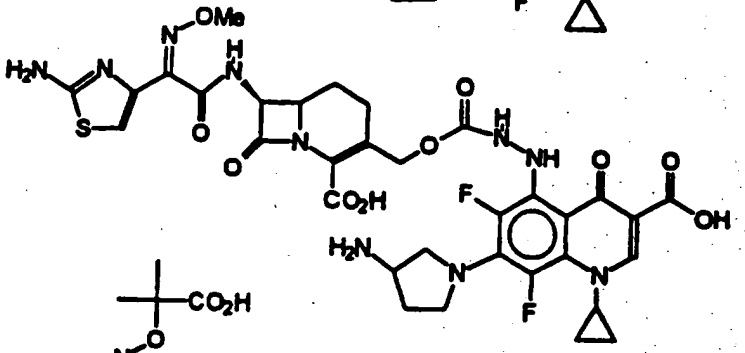


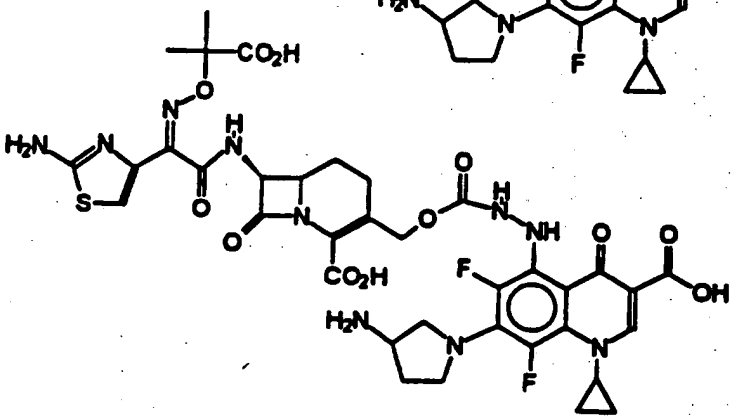


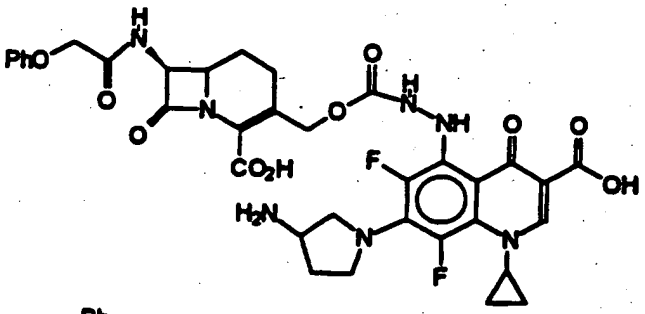


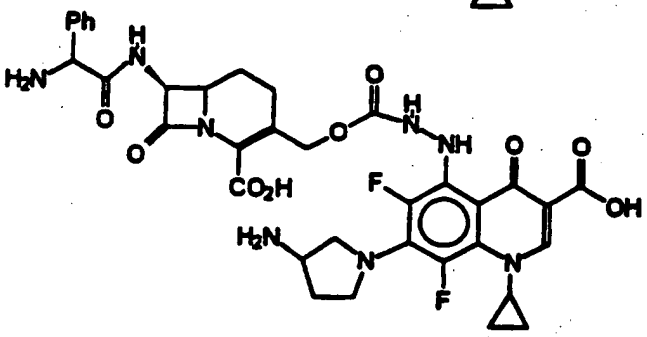


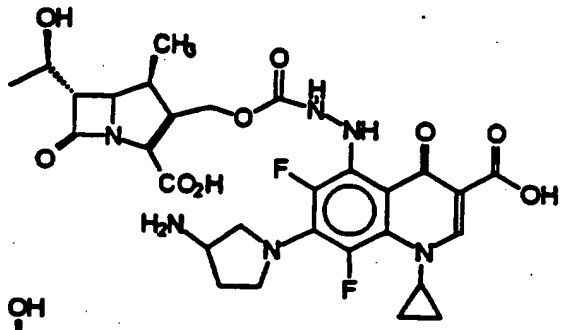


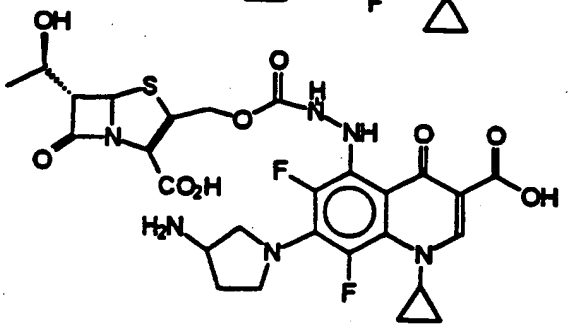


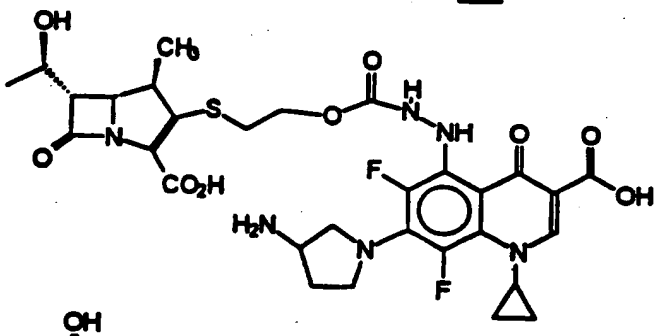


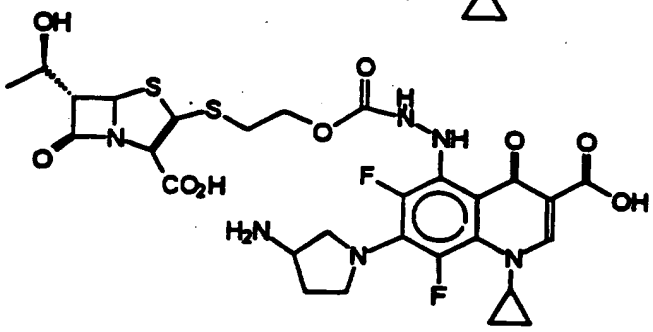


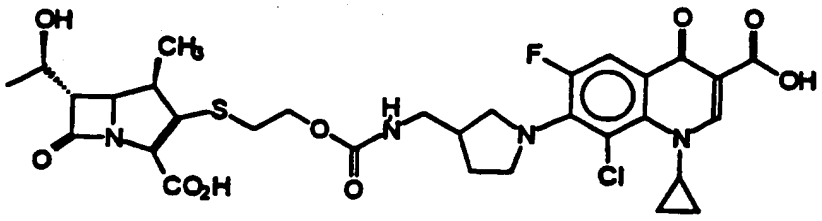






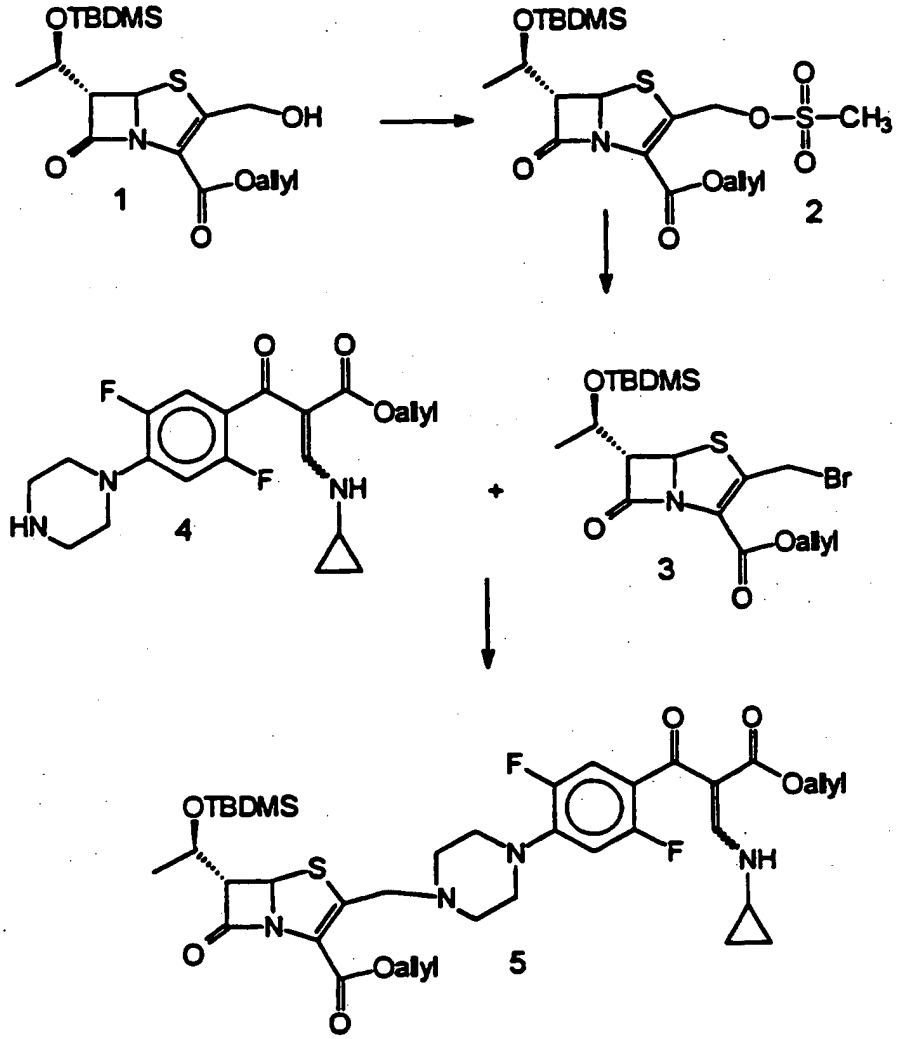


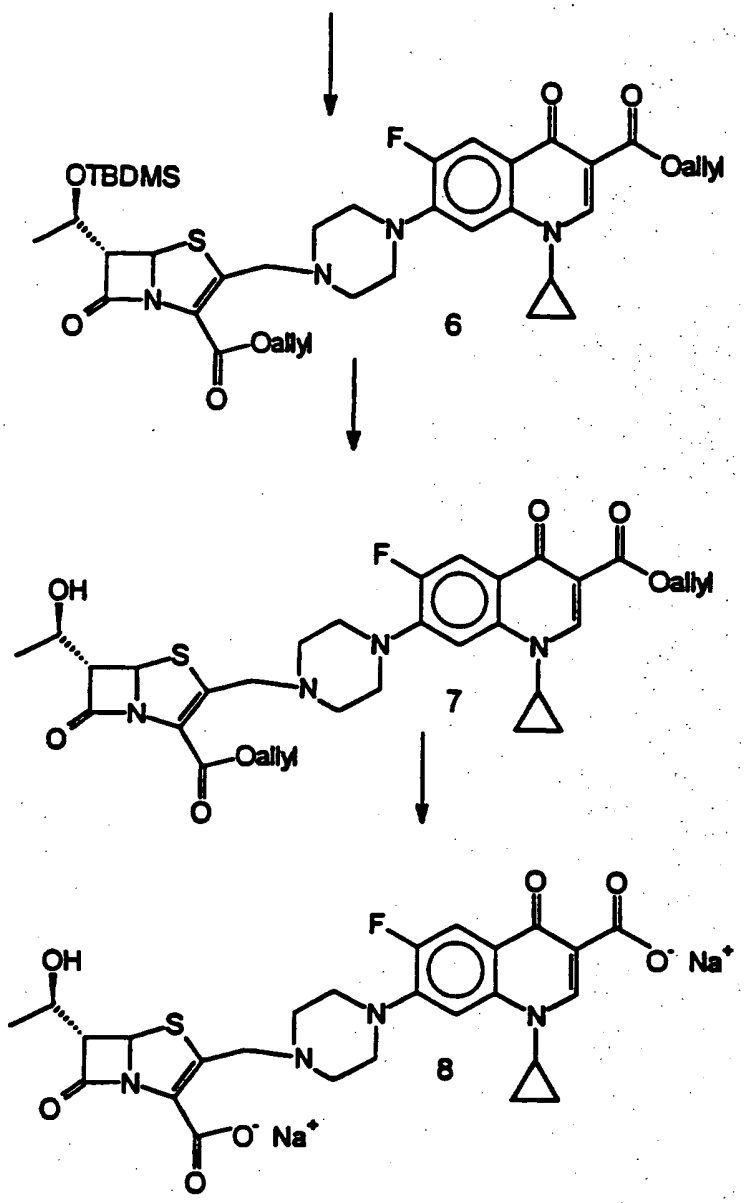




Example 6

Synthesis of [5R-[5α,6α(R*)]]-3-[[4-(3-Carboxy-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-quinolinyl)-1-piperazinyl]methyl]-6-(1-hydroxyethyl)-7-oxo-4-thia-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic Acid, Disodium Salt.





To a cooled (0°C) solution of Compound 1 (4.2 g), prepared according to U. S. Patent 4,631,150, Battistini et al., issued December 23, 1986 (incorporated by reference herein), in CH_2Cl_2 (75 mL) is added methanesulfonyl chloride (1.05 mL), dropwise, followed by the dropwise addition of triethylamine (1.43 mL), under N_2. The mixture is stirred at 0°C for 40 minutes whereupon a 5% solution of $NaHCO_3$ (60 mL) is added. After stirring at 0°C for 10 minutes, the organic layer is separated and washed with dilute brin (2 x 30 mL). The organic porti n is dried (Na_2SO_4) and the volatiles are removed in vacuo to provide Compound 2.

To a solution of Compound 2 (4.3 g) in DMSO (40 mL) is slowly added a solution of $CaBr_2$ (1.89 g) in DMSO (38 mL), under N_2. The reaction mixture is

stirred for 3 hours, whereupon the mixture is diluted with EtOAc (175 mL) and poured over an ice/water mixture (175 mL). The mixture is stirred for 5 minutes whereupon the organic layer is separated and the aqueous layer is extracted with EtOAc (2 x 40 mL). The organic portion is washed with brine (2 x 60 mL) and dried (Na_2SO_4). The solvents are removed in vacuo to provide Compound 3.

To a solution of Compound 4 (1.9 g), prepared in the same manner as Compound 5 in Example 2, in a 1:1 mixture of DMF and CH_2Cl_2 (60 mL) is slowly added a solution of Compound 3 (2.32 g) in a 1:1 mixture of DMF and CH_2Cl_2 (30 mL), under N_2. N,N-Diisopropylethylamine (0.98 mL) is added dropwise and the reaction is allowed to stir at ambient temperature until complete. Upon completion, methanol (15 mL) is added and the mixture is stirred for 15 minutes. The volatiles are removed in vacuo until a small amount of DMF remains whereupon methanol (150 mL) is added. The mixture is stirred for 5 minutes and filtered to obtain Compound 5.

To a solution of Compound 5 (2.2 g) in CH_3CN (35 mL) is added N,O-bis(trimethylsilyl)acetamide (2.17 mL). The reaction mixture is stirred under N_2 at ambient temperature until complete. The reaction is quenched with water (30 mL), and the resulting slurry is filtered and washed with a mixture of water and CH_3CN (5:1) giving Compound 6.

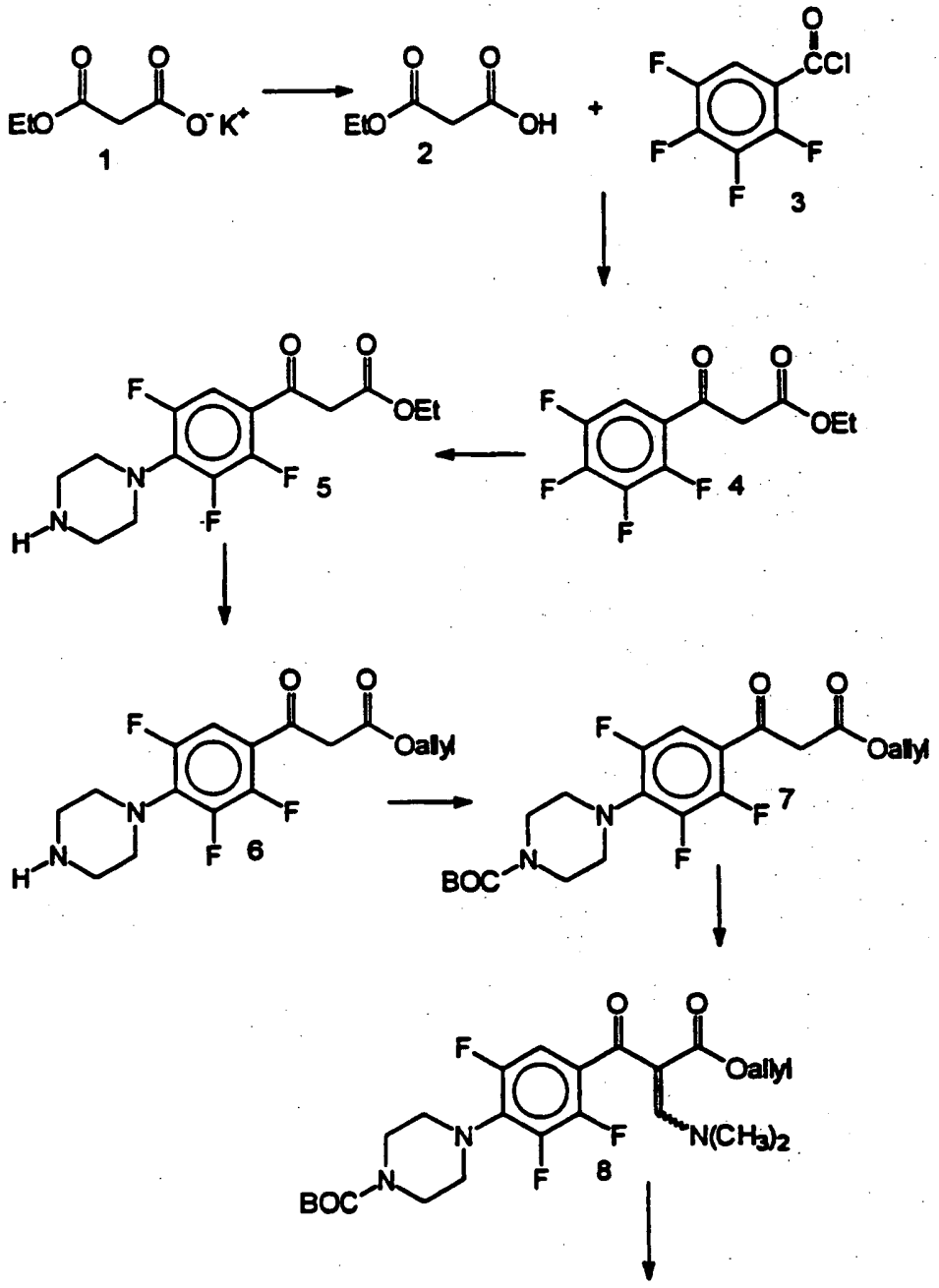
To a solution of Compound 6 (1.7 g) in THF (15 mL) and acetic acid (1.18 mL) is added tetra-n-butyl ammonium fluoride (5.76 mL of a 1M solution in THF), under N_2. The mixture is stirred at ambient temperature overnight and, upon completion, is diluted with ether (25 mL). The solution is stirred for a half-hour, allowing the product to crystallize. The slurry is filtered through troyfelt and the solid residue is washed with ether to obtain Compound 7.

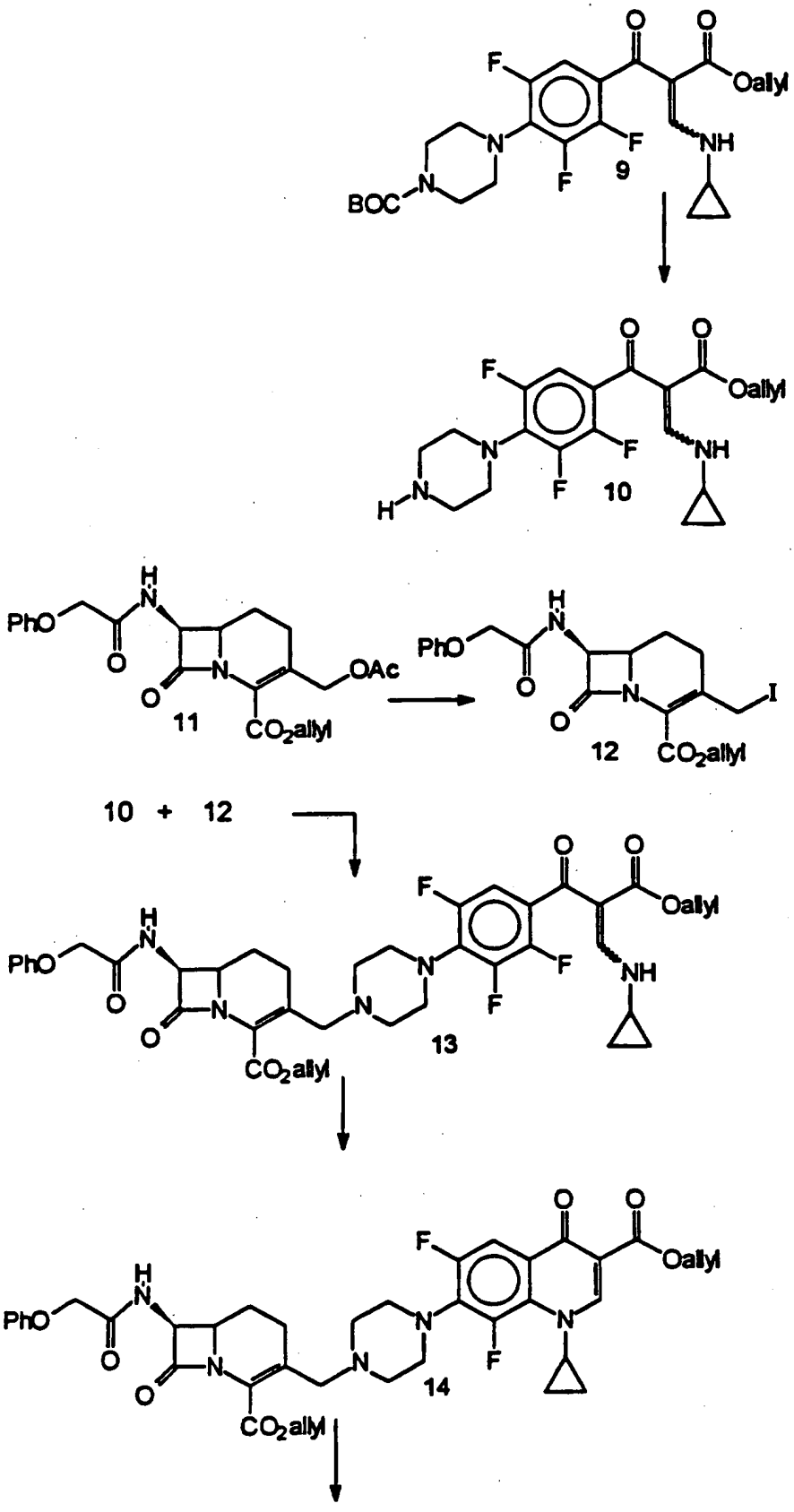
To a solution of Compound 7 (1.32 g) in CH_2Cl_2 (80 mL) is added tetrakis(triphenylphosphine)palladium (0) (227 mg), under N_2. The mixture is cooled (-10 to -5°C) and a cooled solution (<-10°C) of sodium ethylhexanoate (643 mg) in THF (40 mL) is added dropwise. The mixture is stirred f r approximately 30 minutes, whereupon the resulting slurry is filtered and washed successively with CH_2Cl_2 and acetone, to obtain [5R-[5α,6α(R*)]]-3-[[4-(3-Carboxy-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-quinolinyl)-1-piperazinyl]-methyl]-6-(1-hydroxyethyl)-7-oxo-4-thia-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic Acid, Disodium Salt (Compound 8).

Example 7

Synthesis of [6R-[6α,7β]]-3-[[4-(3-Carboxy-1-cyclopropyl-6,8-difluoro-1,4-dihydro-4-oxo-7-quinolinyl)-1-piperazinyl]]methyl]-8-oxo-7-[2-

(phenoxyacetyl)amino]-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic Acid, Disodium Salt.





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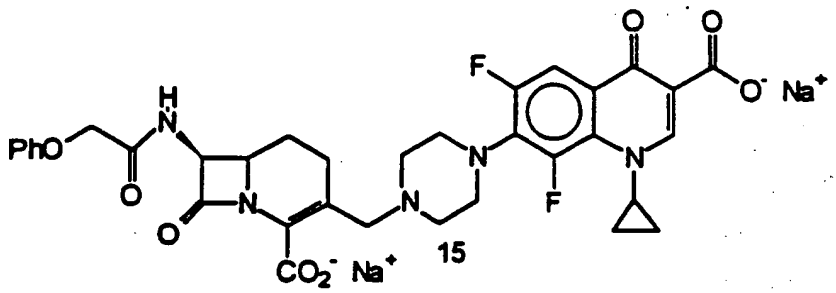

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To a cooled solution of potassium ethyl malonate (20 g) (Compound 1) in water (12.5 mL) is added 12N HCl (10.1 mL) at a rate which allows the temperature to be maintained between 5-10°C. Once the addition is complete, the KCl formed is filtered and rinsed with ether (40 mL). The ethereal portion of the filtrate is separated and the aqueous portion is extracted with Et_2O (3 x 15 mL). The combined ether layers are dried ($MgSO_4$) and the solvent removed in vacuo to give Compound 2.

To a cooled (-30°C) solution of 2,2-biquinoline (7.9 mg) and Compound 2 (8.2 g) in THF (95 mL), under N_2, is added 2.5 M n-BuLi in hexane until a pink color persists at -5°C (approximately 50 mL). The mixture is cooled to -50°C and a solution of 2,3,4,5-tetrafluorobenzoyl chloride (4.0 mL) (Compound 3) in THF (45 mL) is added dropwise so that the temperature is maintained at -50°C. After 30 minutes, the mixture is allowed to warm to ambient temperature and is quenched with 1M HCl (130 mL) at a rate which allows the temperature to be maintained at about 30°C. The organic layer is separated and the aqueous layer is extracted with Et_2O (4 x 40 mL). The combined organic layers are washed with 10% aqueous $NaHCO_3$ (3 x 100 mL) and brine (3 x 100 mL). The organic portion is dried ($MgSO_4$) and treated with activated charcoal. After removal of the solvents in vacuo, the residue obtained is subjected to column chromatography (silica) to give a mixture of Compound 4 and its enol ether which is used directly in the next step.

To a solution of Compound 4 (12.3 g) in THF (240 mL) is added piperazine (16 g). The reaction is heated at reflux, under N_2, until completion, whereupon the volatiles are removed in vacuo. The residue obtained is dissolved in EtOAc (150 mL), washed with water (4 x 50 mL), and dried ($MgSO_4$). The solvent is removed in vacuo and the residue obtained is subjected to column chromatography (silica) to give a mixture of Compound 5 and its enol ether which is used directly in the next step.

To a solution f allyl alcohol (24 mL) in toluene (70 mL) is added 4-dimethylaminopyridine (1.3 g), under N_2. Compound 5 (11.9 g) is added and the mixture is heated to reflux. Upon completion, the reaction mixture is co led and

saturated ammonium chloride (175 mL) is added, followed by the addition of EtOAc (200 mL). The layers are separated and the EtOAc portion is washed with water (4 x 60 mL) and brine (2 x 45 mL), and dried ($MgSO_4$). The solvents are removed in vacuo and the residue is subjected to column chromatography (silica) to provide a mixture of Compound 6 and its enol ether which is used directly in the next step.

To a solution of Compound 6 (10.1 g) in $CHCl_3$ (150 mL) is added a solution of di-t-butylcarbonate (7.5 mL) in $CHCl_3$ (25 mL). The reaction is stirred for 5 minutes under N_2 at ambient temperature and the volatiles are removed in vacuo. Hexanes are added to give Compound 7.

To a solution of Compound 7 (10.6 g) in toluene (40 mL) is added dimethylformamide dimethylacetal (4.9 mL). The reaction is heated at reflux under N_2 for 2 hours and the volatiles are removed in vacuo to give crude Compound 8. The crude compound is carried directly to the next step by dissolving in EtOH (47 mL) and adding cyclopropyl amine (2.65 mL). The mixture is stirred for 2 hours at ambient temperature under N_2. The volatiles are removed in vacuo and the residue is crystallized from 20% EtOAc/hexanes to give Compound 9.

To a cooled solution of Compound 9 (9.1 g) in anisole (70 mL) at 5-10°C is added TFA (70 mL). After stirring for 5 minutes under N_2, the ice bath is removed and the reaction is warmed to ambient temperature. After 2 hours, most of the TFA and some of the anisole is removed in vacuo. The residue is slurried in Et_2O (250 mL) and filtered. The solid is dissolved in a mixture of CH_2Cl_2 (100 mL) and saturated $NaHCO_3$ (100 mL) and stirred for 10 min. The CH_2Cl_2 portion is separated, dried ($MgSO_4$), and treated with activated charcoal. The volatiles are removed in vacuo and the residue obtained is crystallized with hexane to give Compound 10.

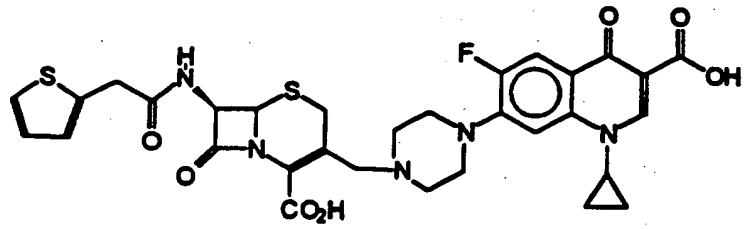
To a cooled (0°C) solution of allyl (7S, 6R)-7-(phenoxyacetamido)-3-(acetoxymethyl)-1-carba-1-dethia-3-cephem-4-carboxylate (4.2 g)(Compound 11), prepared as described in L. Blaszczak et al., 33 J. Am. Chem. Soc. 1656 (1990), in CH_2Cl_2 (30 mL) is added iodotrimethylsilane (2.07 mL). The mixture is stirred at 0°C for 0.5 hour and then at ambient temperature for 1 hour. The volatiles are removed in vacuo to provide crude Compound 12 which is used directly in the next step. In a second vessel, to a solution of Compound 10 (4 g) in DMF (30 mL) and CH_2Cl_2 (30 mL) is added activated molecular sieves (1 g), under N_2. After stirring for 30 minutes, the solution is transferred to a third vessel and diisopropylethylamine (1.72 mL) is added, under N_2. The mixture is c oled (-40°C) and, after stirring for 0.5 hour, a solution of the forementioned crude Compound 12 in DMF (30 mL) and CH_2Cl_2 (30 mL) is slowly added. The mixture

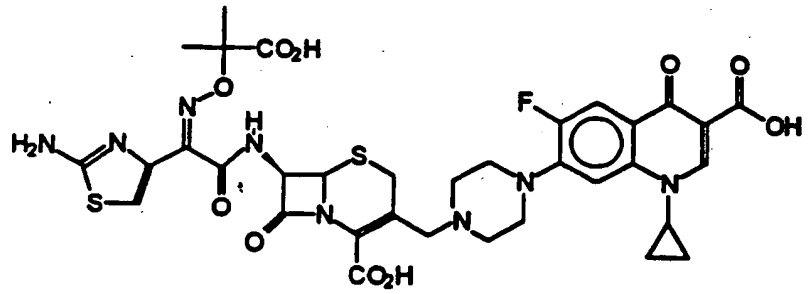
is stirred for 1 hour at -40°C and then stirred at 0°C for 1 hour and all wed to warm to ambient temperature. Upon completion, the reaction is diluted with CH_2Cl_2 (100 mL) and washed with 1M HCl (2 x 80 mL) and brine (2 x 80 mL). The organic portion is separated and the solvents are removed in vacuo to provide a residue that is subjected to column chromatography (silica) to provide Compound 13.

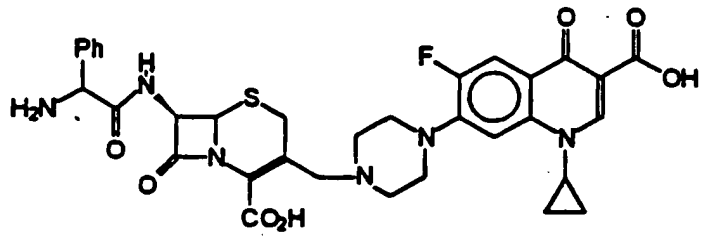
To a solution of Compound 13 (4.1 g) in CH_3CN (60 mL) is added N,O-bis(trimethylsilyl)acetamide (3.9 mL). The reaction mixture is stirred under N_2 at ambient temperature until complete. The reaction is quenched with water (60 mL), and the resulting slurry is filtered and washed with a mixture of water and CH_3CN (5:1) to provide Compound 14.

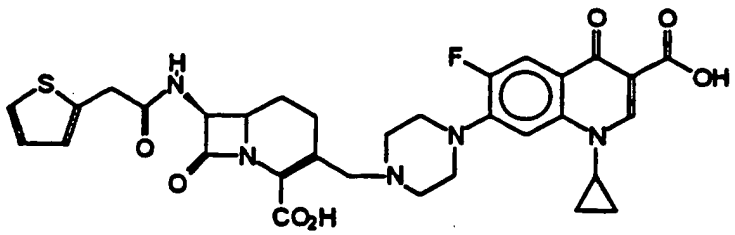
To a solution of Compound 14 (3.8 g) in CH_2Cl_2 (210 mL) is added tetrakis(triphenylphosphine)palladium (0) (580 mg), under N_2. The mixture is cooled (-10 to -5°C) and a cooled solution (<-10°C) of sodium ethylhexanoate (1.67 mg) in THF (105 mL) is added dropwise. The mixture is stirred for approximately 30 minutes, whereupon the resulting slurry is filtered and washed successively with CH_2Cl_2 and acetone, to obtain [6R-[6α,7β]]-3-[[4-(3-Carboxy-1-cyclopropyl-6,8-difluoro-1,4-dihydro-4-oxo-7-quinolinyl)-1-piperazinyl]]-methyl]-8-oxo-7-[2-(phenoxyacetyl)amino]-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic Acid, Disodium Salt (Compound 15).

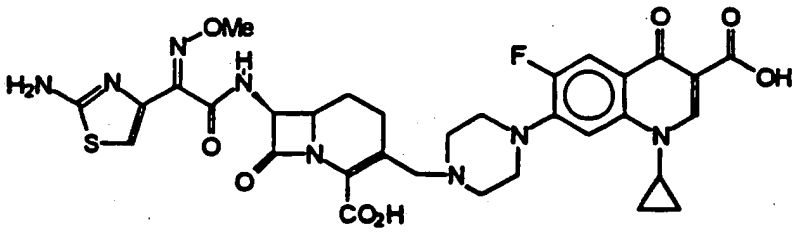
The following compounds are prepared according to Examples 6 and 7, with substantially similar results.

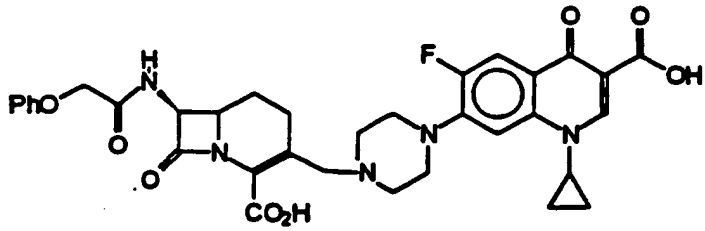


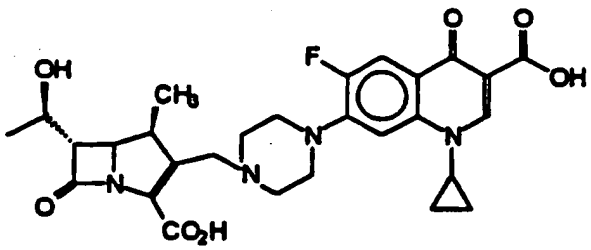


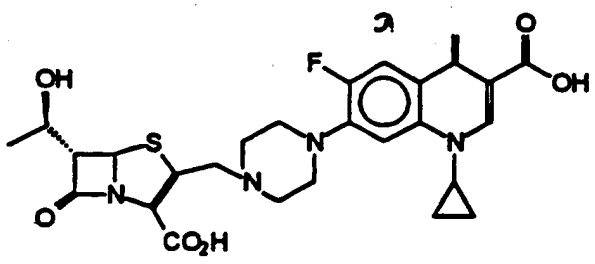


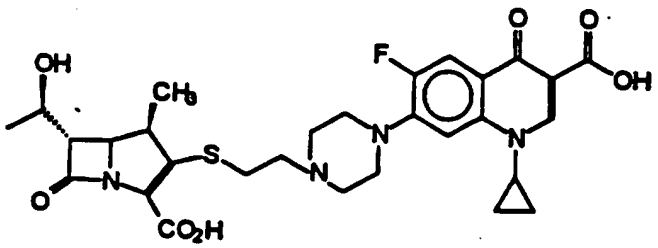


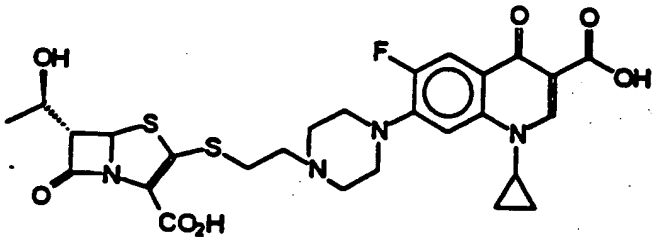


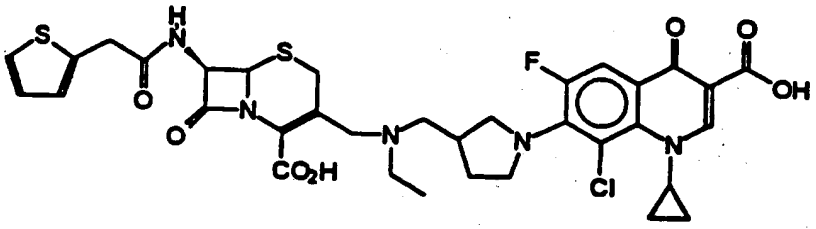


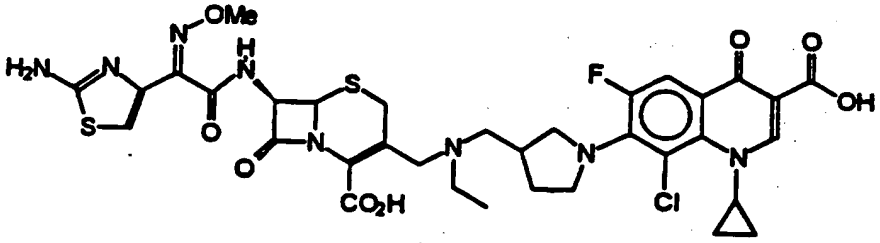


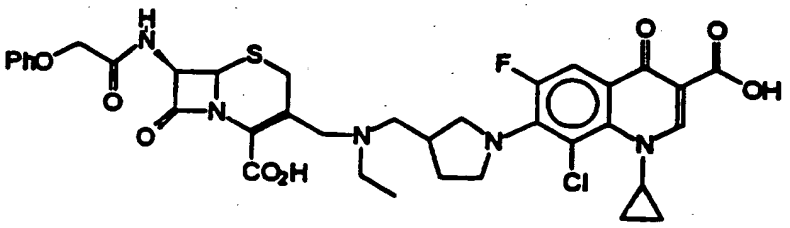


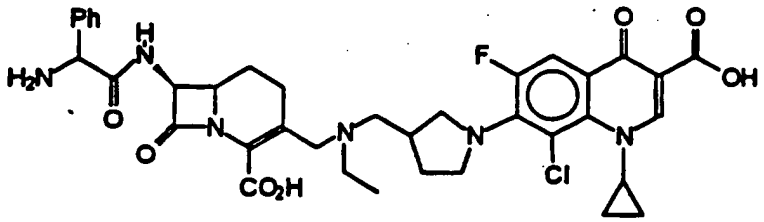


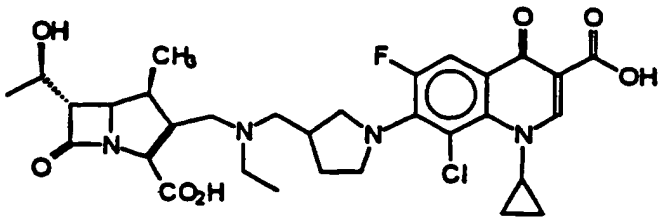


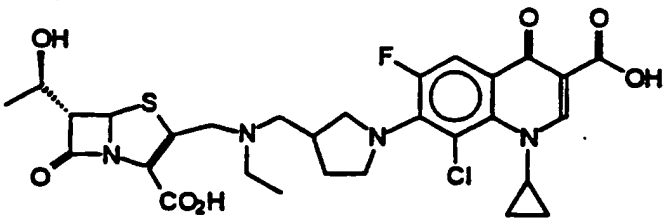


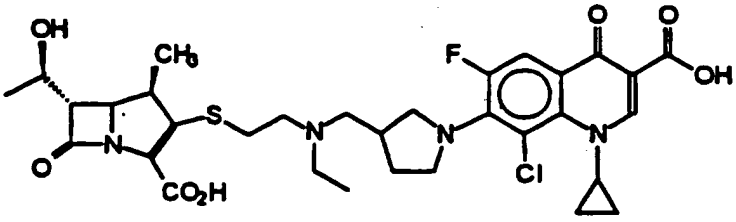


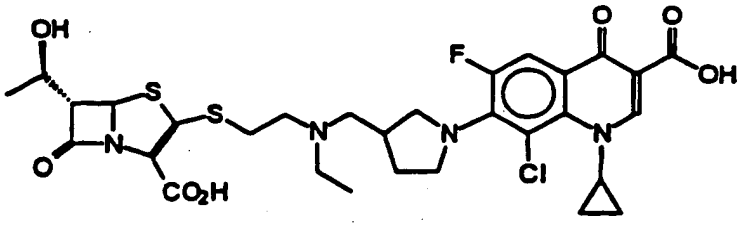


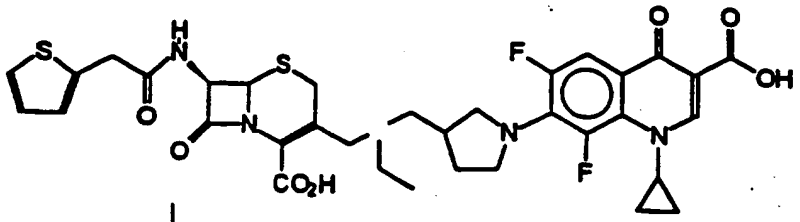


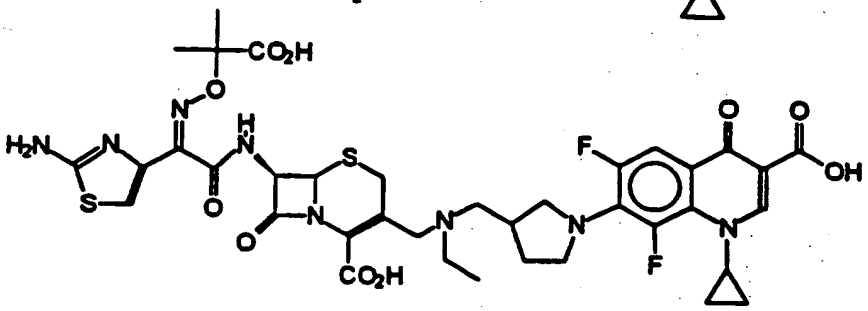


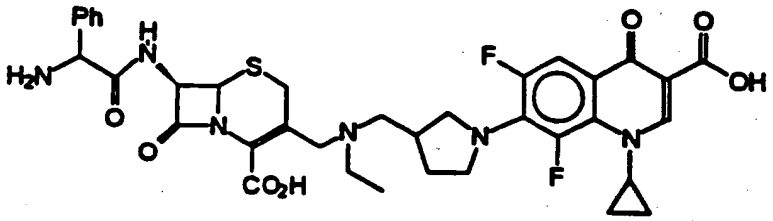


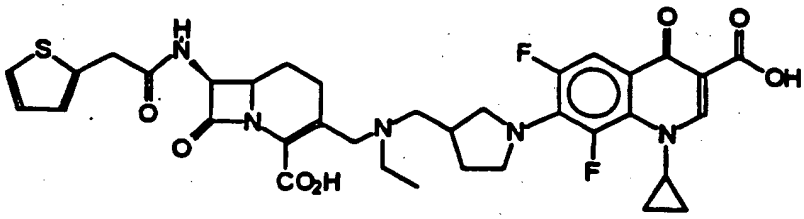


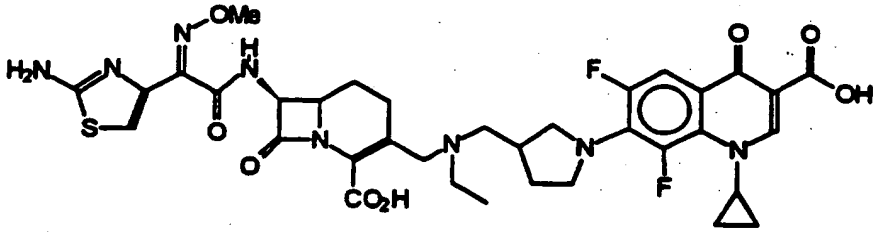


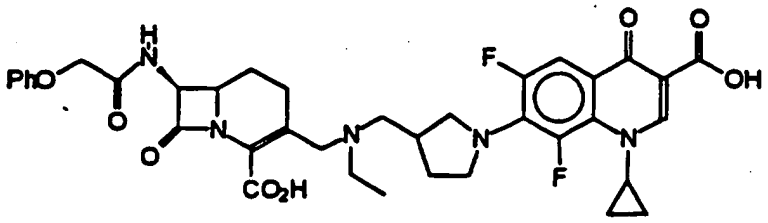


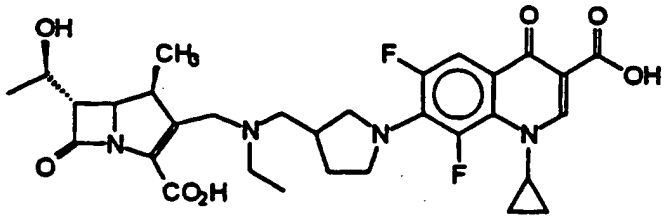


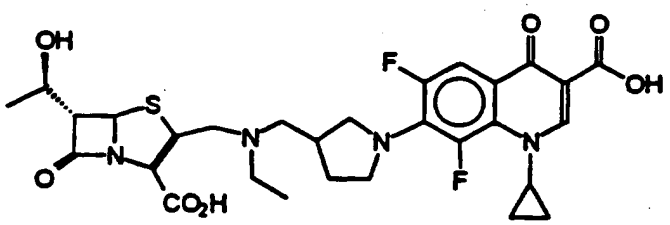


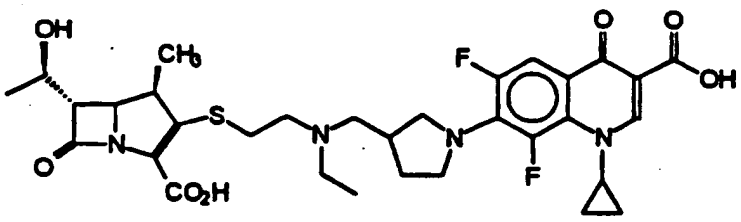


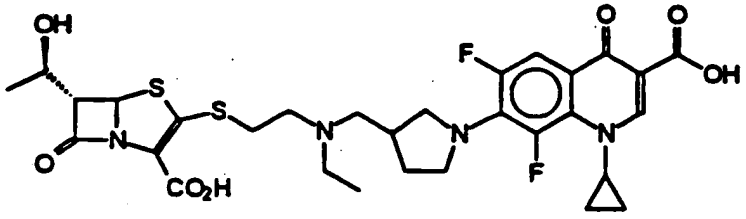


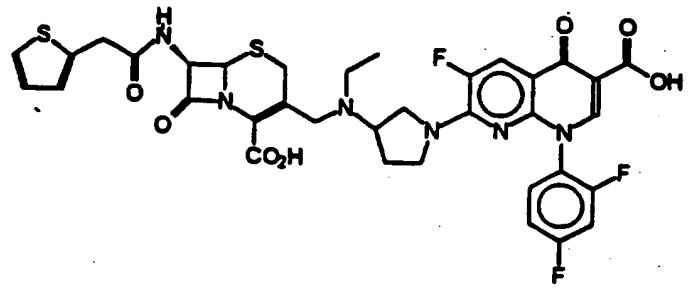


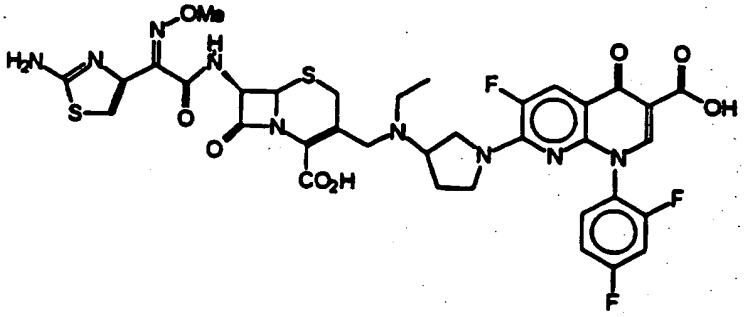


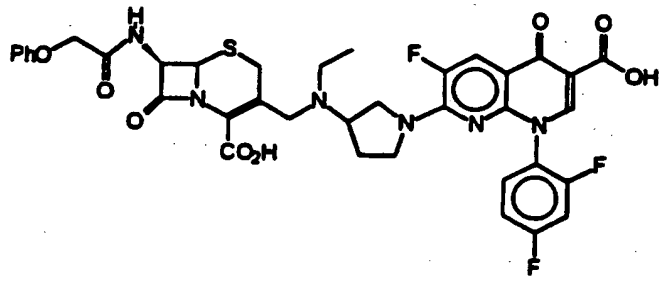


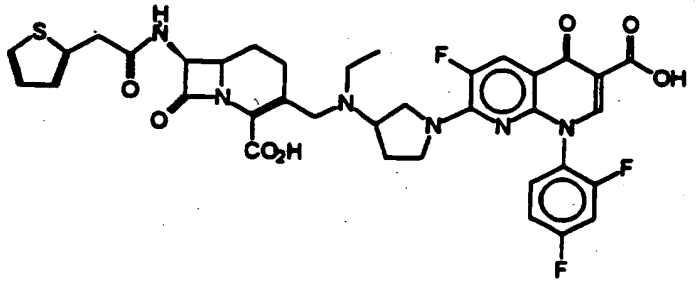


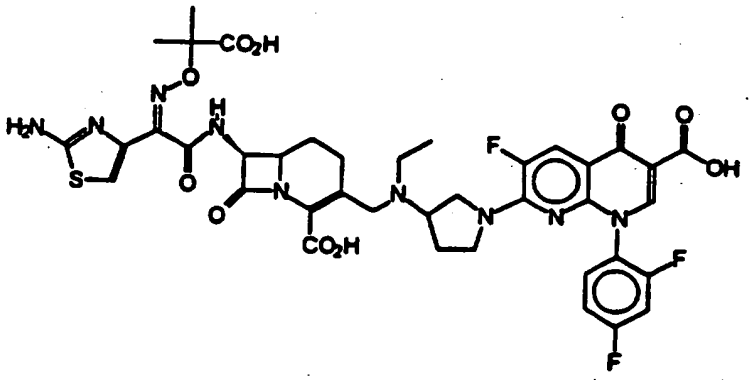


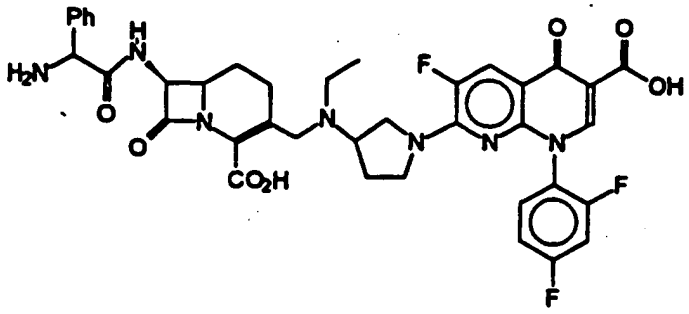


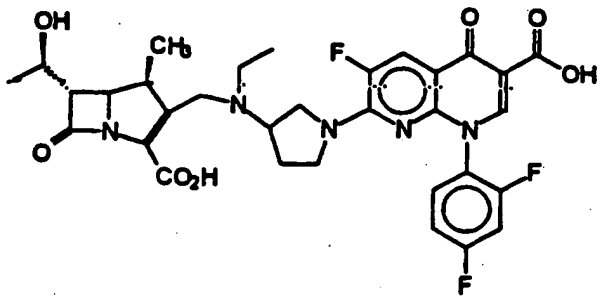


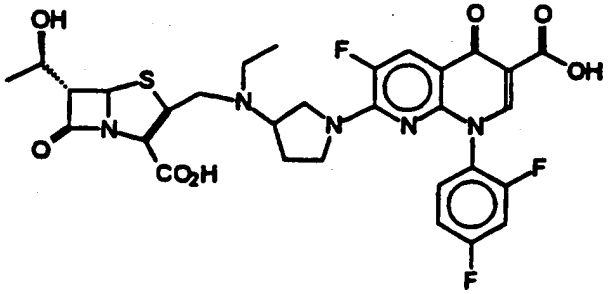


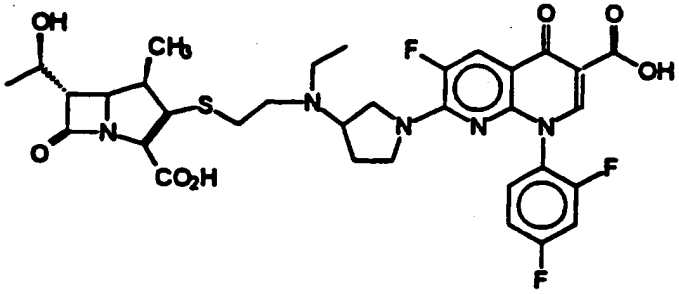


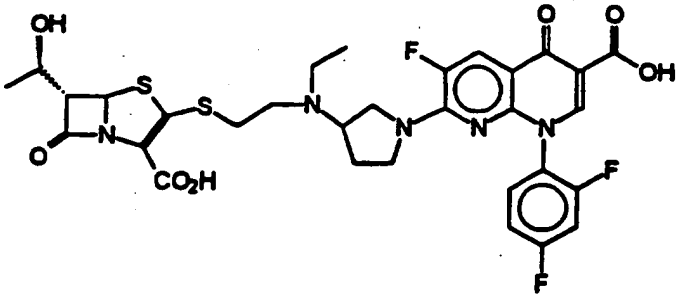


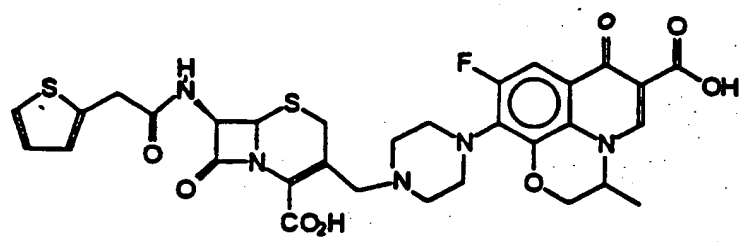


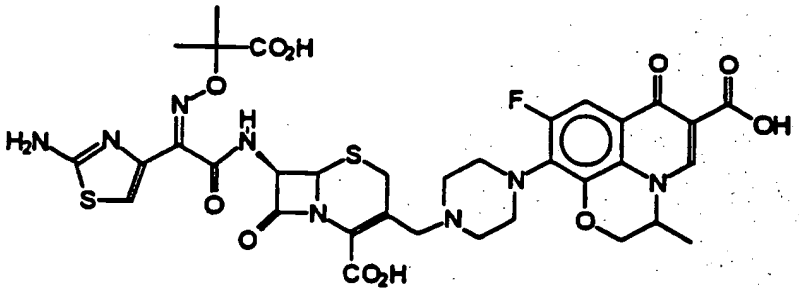


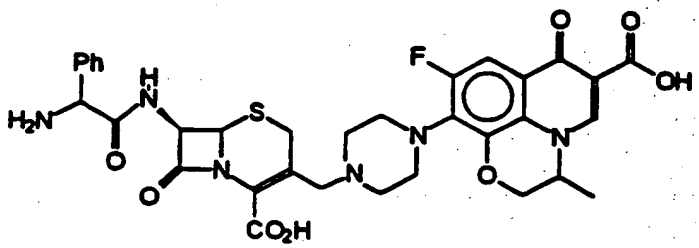


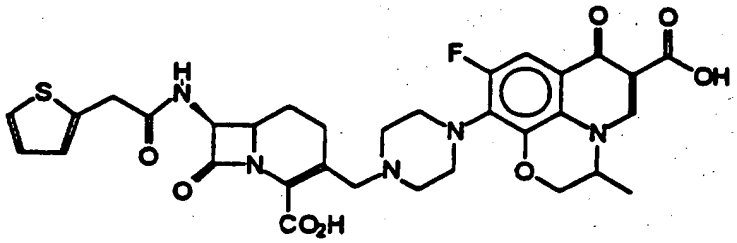


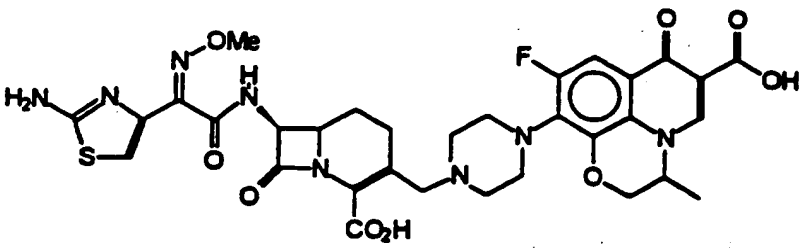


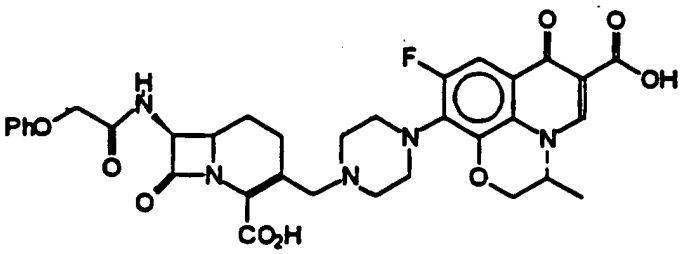


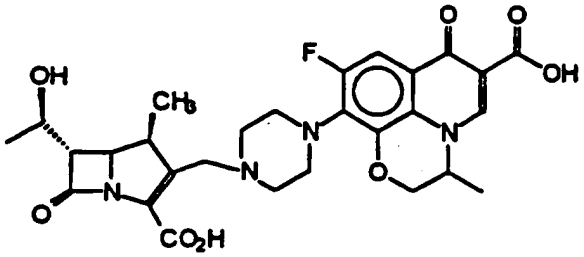


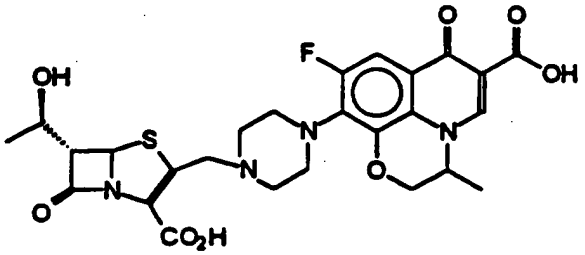


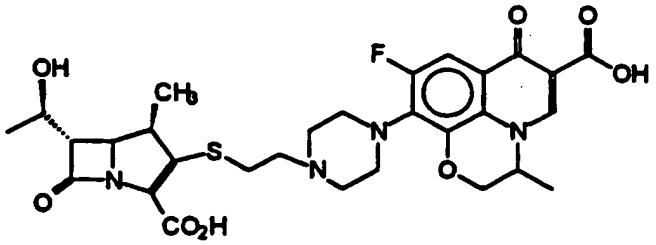


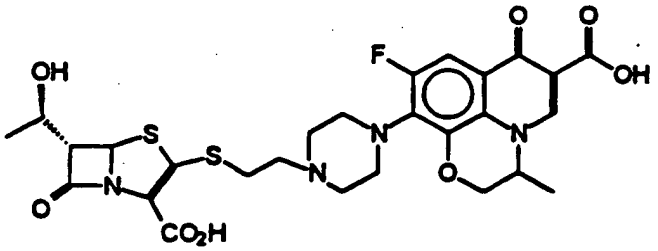


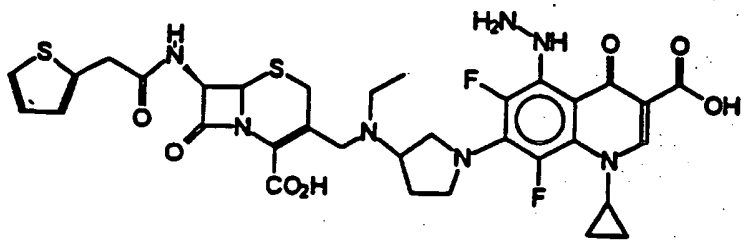


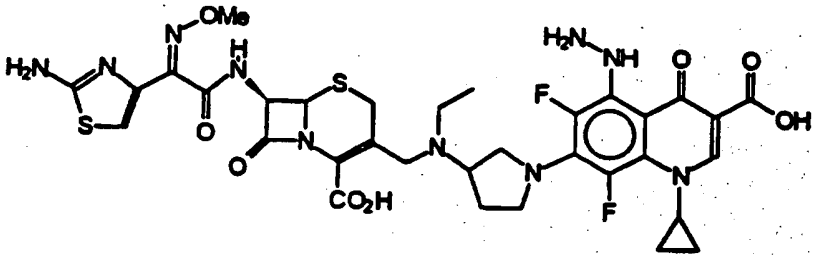


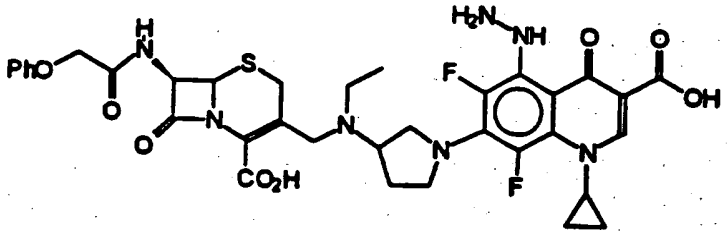


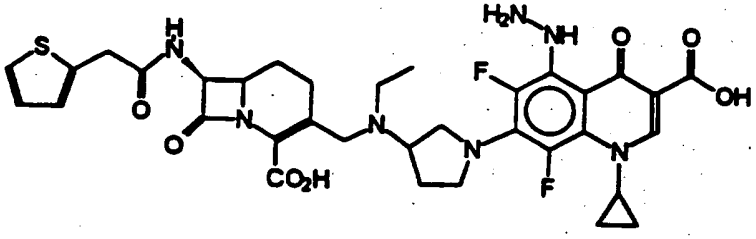


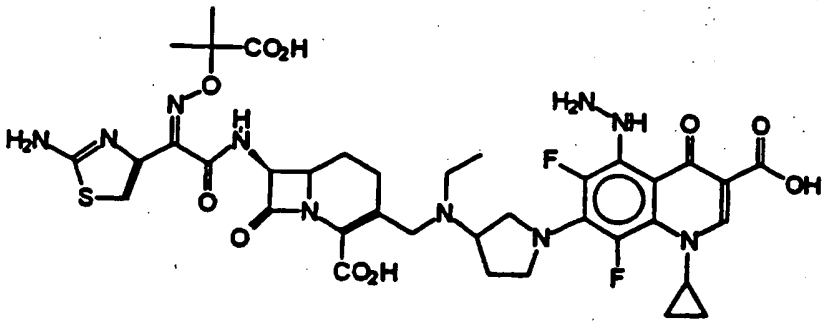


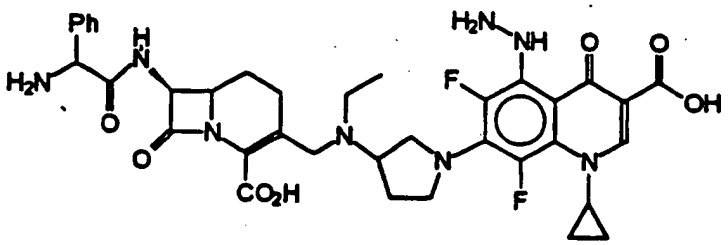


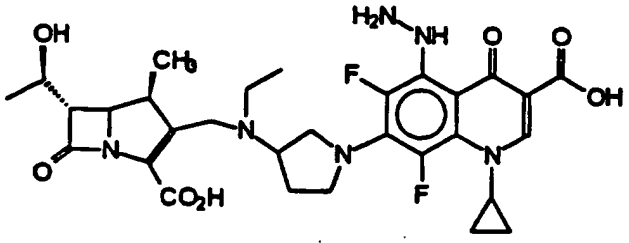


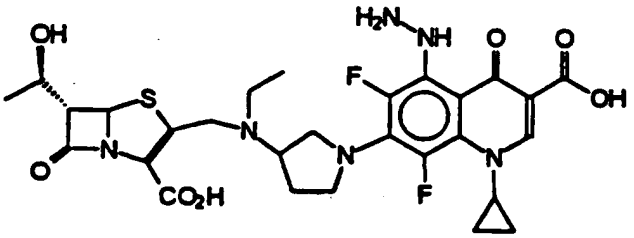


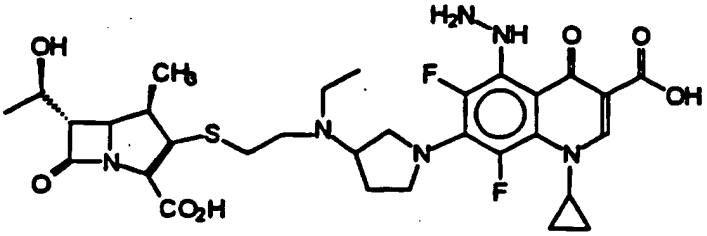


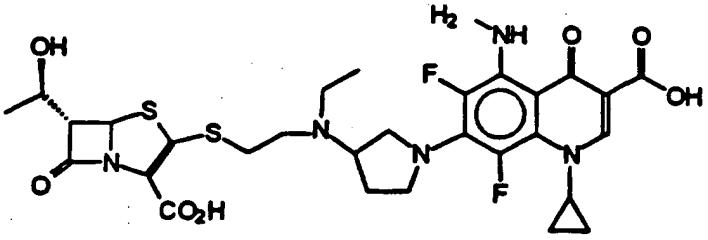


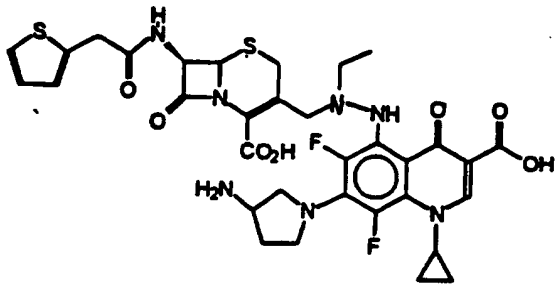


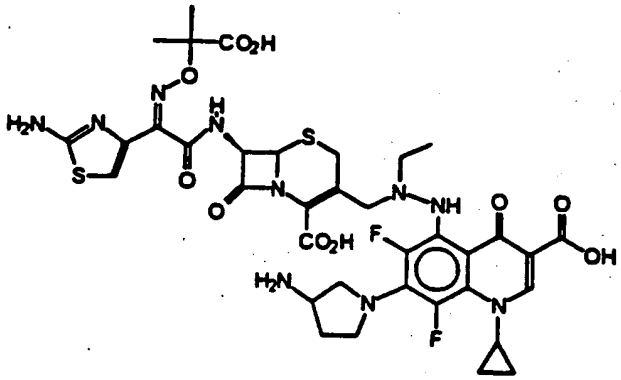


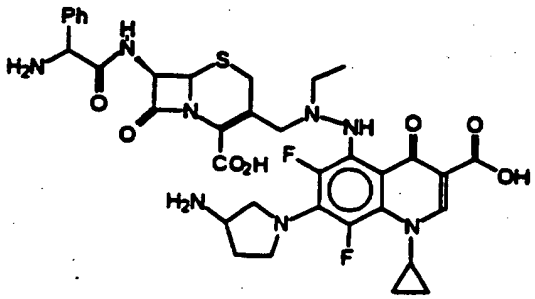


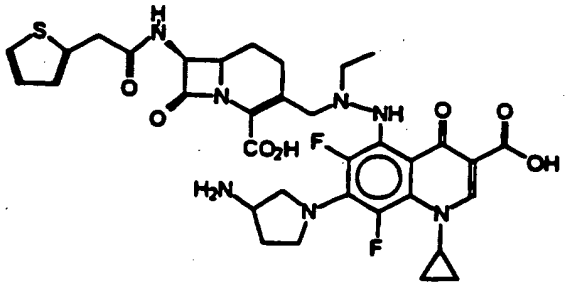


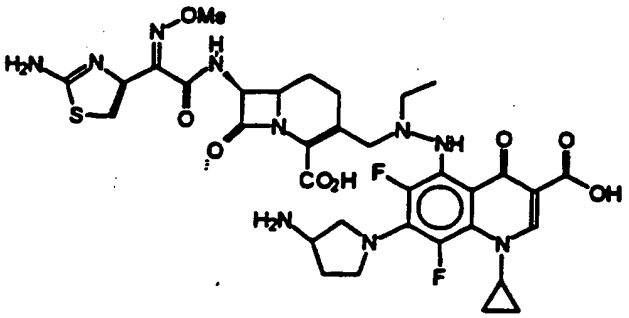


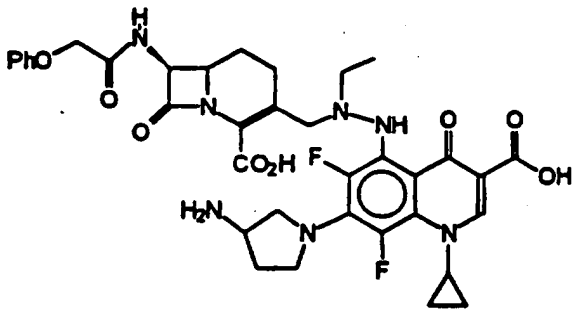


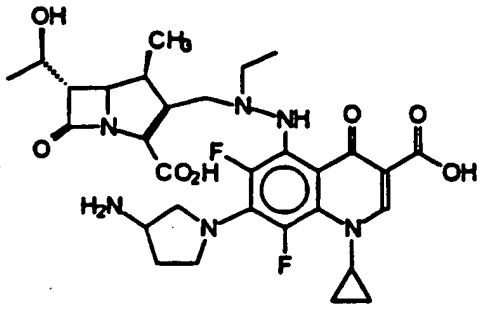


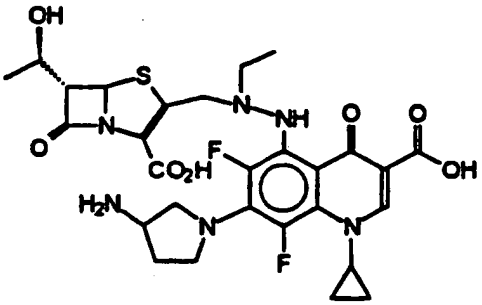


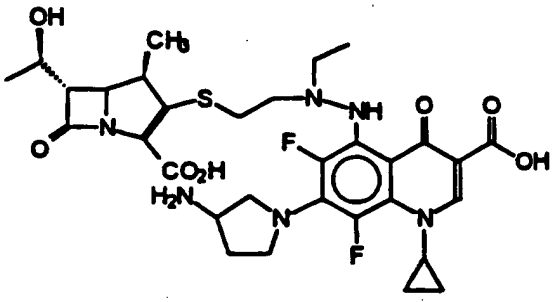


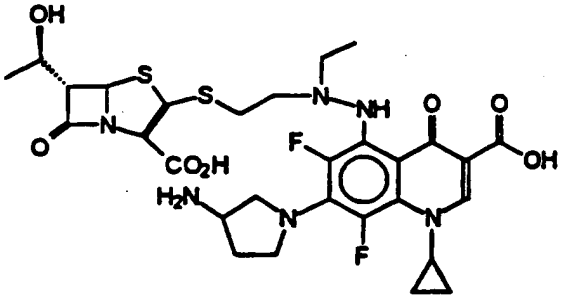


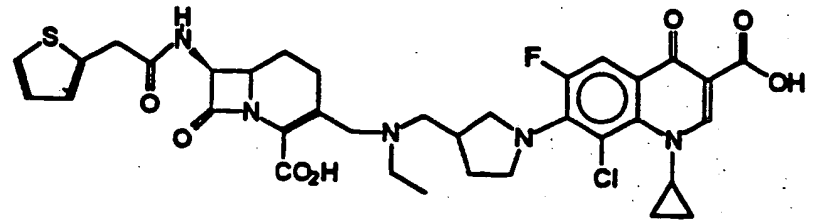


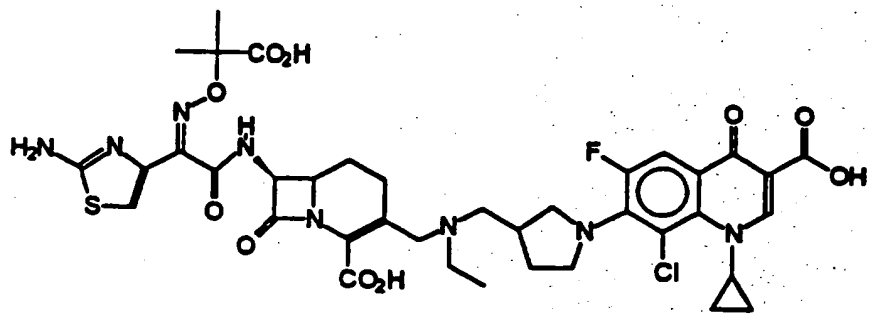






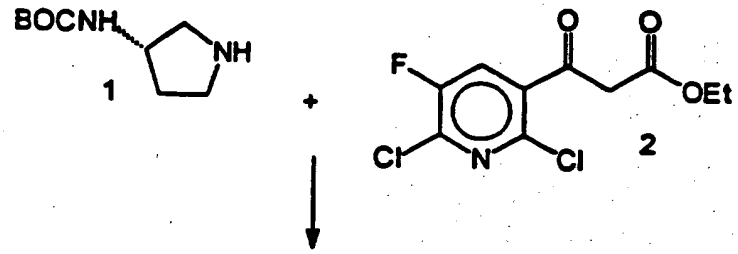


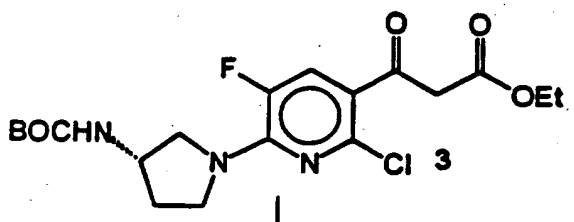


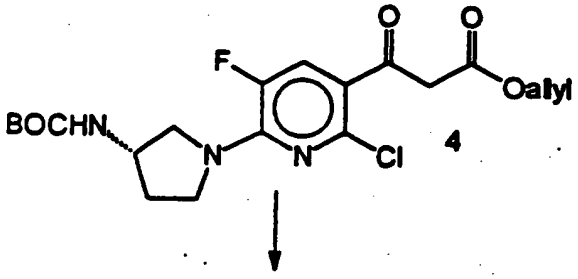


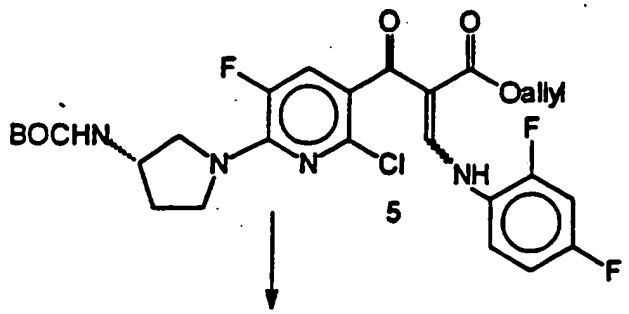
Example 8

Synthesis of [4S-[3(R*),4α,5β,6β(S*)]]-3-[[[1-[3-Carboxy-1-(2,4-difluorophenyl)-6-fluoro-1,4-dihydro-4-oxo-1,8-napthyridin-7-yl]-3-pyrrolidinyl]amino]methyl]-6-(1-hydroxyethyl)-4-methyl-7-oxo-1-azabicyclo-[3.2.0]hept-2-ene-2-carboxylic Acid, Disodium salt





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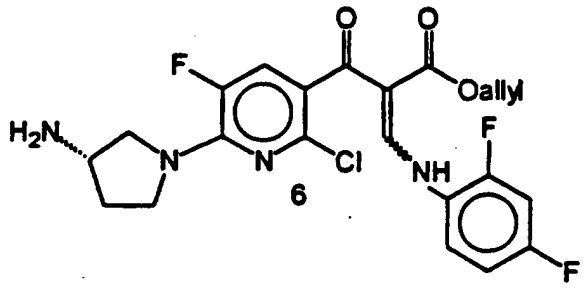
O
O
Oallyl
N
N
Cl
NH
F
F
5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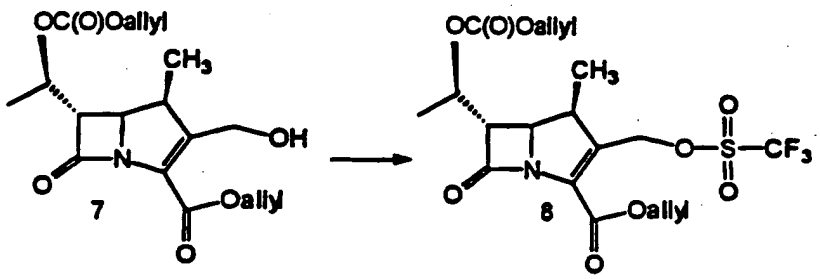
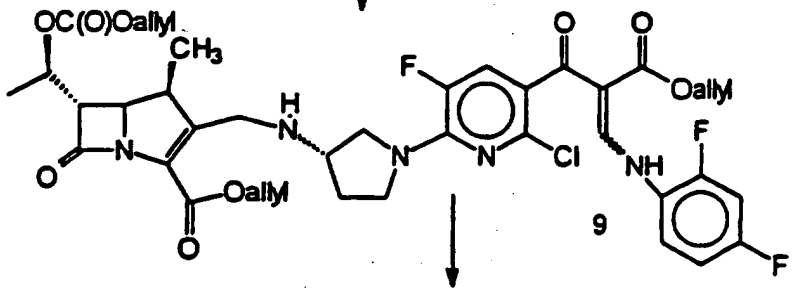
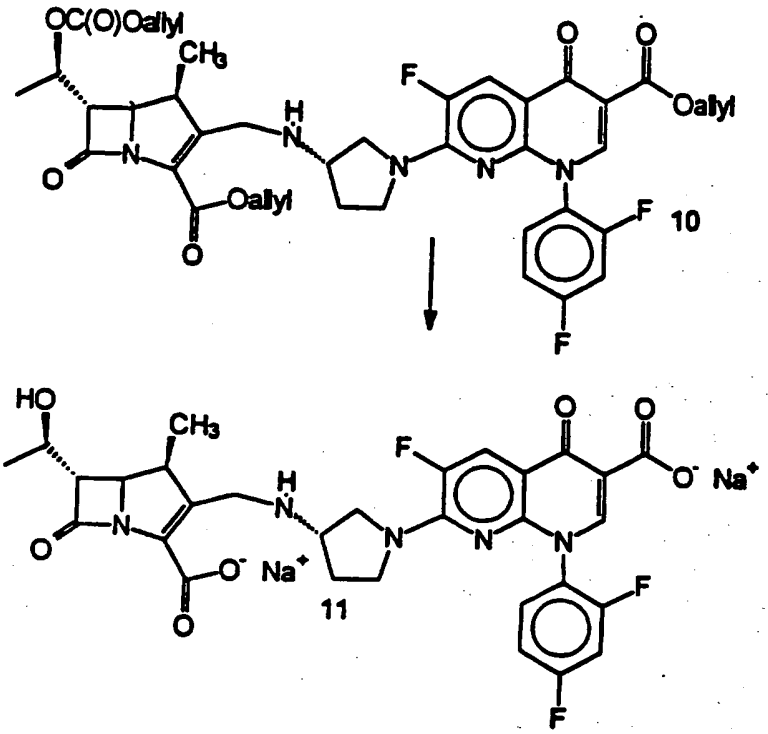
O
O
Oallyl
N
N
Cl
NH
F
F
6


OC(O)Oallyl
CH3
OH
N
O
Oallyl
O
7
OC(O)Oallyl
CH3
O
S
CF3
O
O
N
O
Oallyl
O
8

6 + 8


OC(O)Oallyl
CH3
H
N
N
O
Oallyl
O
F
O
O
Oallyl
N
Cl
NH
F
F
9



10 11

To a solution of Compound 2 (12.5 g) (prepared in the same manner as Compound 5 in Example 5 above) is added (S)-(-)-3-(tert-butoxycarbonylamino)pyrrolidine (33.25 g) (Compound 1). The mixture is refluxed under N_2 until complete and the THF is removed under reduced pressure. The residue is slurried in EtOAc (125 mL), and the excess pyrrolidine is filtered ff and rinsed with EtOAc. The EtOAc filtrate is washed with water (2 x 125 mL) and the combined aqueous layers are extracted with EtOAc (70 mL). The combined EtOAc layers are dried ($MgSO_4$) and treated with activated charcoal. The solvents are evaporated in vacuo and the residue is crystallized from isopropyl ether to give Compound 3.

To a solution of allyl alcohol (17 mL) in toluene (75 mL) is added 4-dimethylaminopyridine (0.95 g), under N_2. Compound 3 (13.1 g) is added and the mixture is heated to reflux. Upon completion, the reaction mixture is cooled and saturated ammonium chloride (125 mL) is added, followed by the addition of EtOAc (150 mL). The layers are separated and the EtOAc portion is washed with water (4 x 50 mL) and brine (2 x 40 mL), and dried ($MgSO_4$). The solvents are removed in vacuo and the residue is subjected to column chromatography (silica) to provide Compound 4.

To a solution of Compound 4 (8.65 g) in triethylorthoformate (4.6 mL) is added acetic anhydride (14.6 mL). The mixture is fitted with a Dean-Stark trap and stirred at 130°C for 1.5 h urs under N_2. The volatiles removed in vacuo and the

residue is dissolved in CH_2Cl_2 (30 mL). The solution obtained is cooled t 0 C and 2,4-difluoroaniline is added (2.4 mL). The reaction is stirred at 0°C for 5 minutes under N_2, allowed to warm to ambient temperature and stirred for 1 hour. The volatiles are removed in vacuo and the residue obtained is subjected to column chromatography (silica) to provide Compound 5.

To a cooled solution of Compound 5 (6.1 g) in anisole (40 mL) at 5-10°C is added TFA (40 mL). After stirring for 5 minutes under N_2, the ice bath is removed and the reaction is warmed to ambient temperature. After 2 hours, most of the TFA and some of the anisole is removed in vacuo. The residue is slurried in Et_2O (125 mL) and filtered. The solid is dissolved in a mixture of CH_2Cl_2 (75 mL) and saturated $NaHCO_3$ (50 mL) and stirred for 10 min. The CH_2Cl_2 portion is separated, dried ($MgSO_4$), treated with activated charcoal, and evaporated in vacuo. The residue is crystallized with hexane to give Compound 6.

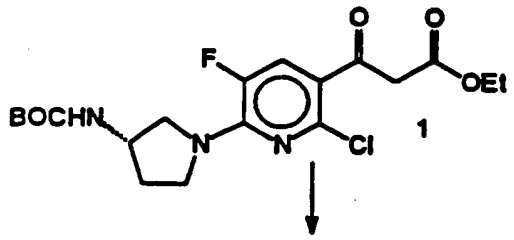
To a cooled (-78°C) solution of Compound 7 (3.56 g), prepared as described in Schmitt et al., J. Antibiot., 41, 780-787, 1988 (incorporated by reference herein), in CH_2Cl_2 (14 mL) is added diisopropylethylamine (1.54 mL), followed by the dropwise addition of trifluoroacetic anhydride (1.49 mL). The reaction is stirred at -78°C for 1.5 hours to provide Compound 8 which is reacted in situ by the dropwise addition of a solution of Compound 6 (4.9 g) and diisopropylethylamine (1.54 mL) in CH_2Cl_2 (18 mL). The reaction is stirred at -78°C until completion, whereupon the cooling bath is removed and water (2 mL) is slowly added. When the temperature reaches -40°C, more water (40 mL) and CH_2Cl_2 (150 mL) is added. The mixture is quickly separated and the organic portion is quickly washed successively with cold water (2 x 50 mL), 10% $NaHCO_3$ (3 x 50 mL) and water (50 mL). The organic portion is dried (Na_2SO_4) and the volatiles are removed in vacuo. The residue obtained is subjected to column chromatography (silica) to obtain Compound 9.

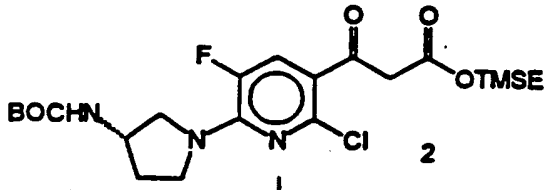
To a solution of Compound 9 (4.1 g) in CH_3CN (55 mL) is added N,O-bis(trimethylsilyl)acetamide (3.35 mL). The reaction mixture is stirred under N_2 at ambient temperature until complete. The reaction is quenched with water (55 mL), and the resulting slurry is filtered and washed with a mixture of water and CH_3CN (5:1) giving Compound 10.

To a solution of Compound 10 (3.3 g) in CH_2Cl_2 (160 mL) is added tetrakis(triphenylphosphine)palladium (0) (433 mg), under N_2. The mixture is cooled (-10 to - 5°C) and a cooled solution (<-10°C) of sodium ethylhexanoate (1.25 g) in THF (80 mL) is added dropwise. The mixture is stirred f r approximately 30 minutes, whereupon the resulting slurry is filtered and washed successively with CH_2Cl_2 and acetone to pr vide Compound 11.

Example 9

Synthesis f [6R-[3(S),6α,7β]]-3-[[[1-[3-Carboxy-1-(1,1-dimethylethyl)-6-fluoro-1,4-dihydro-4-oxo-1,8-napthyridin-7-yl]-3-pyrrolidinyl]amino]methyl]-8-oxo-7-[(2-thienylacetyl)amino]-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic Acid





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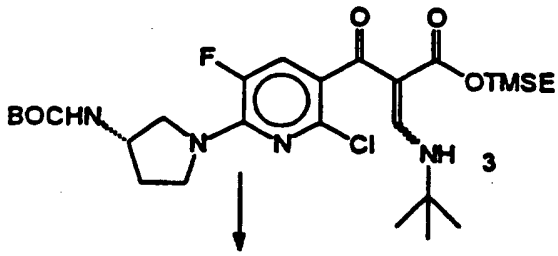
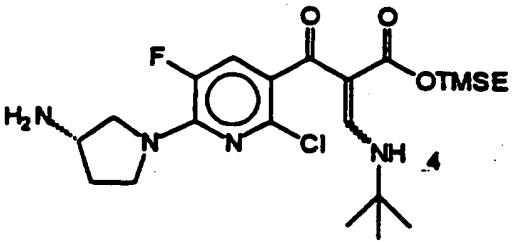
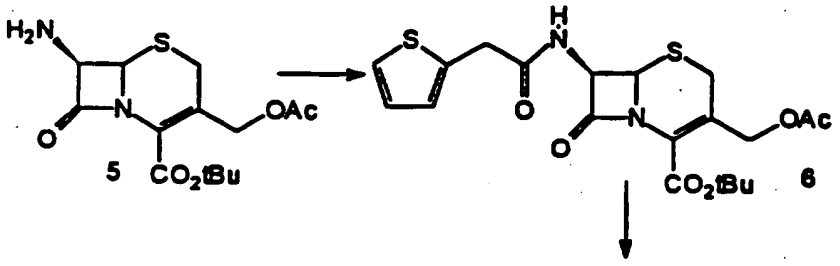
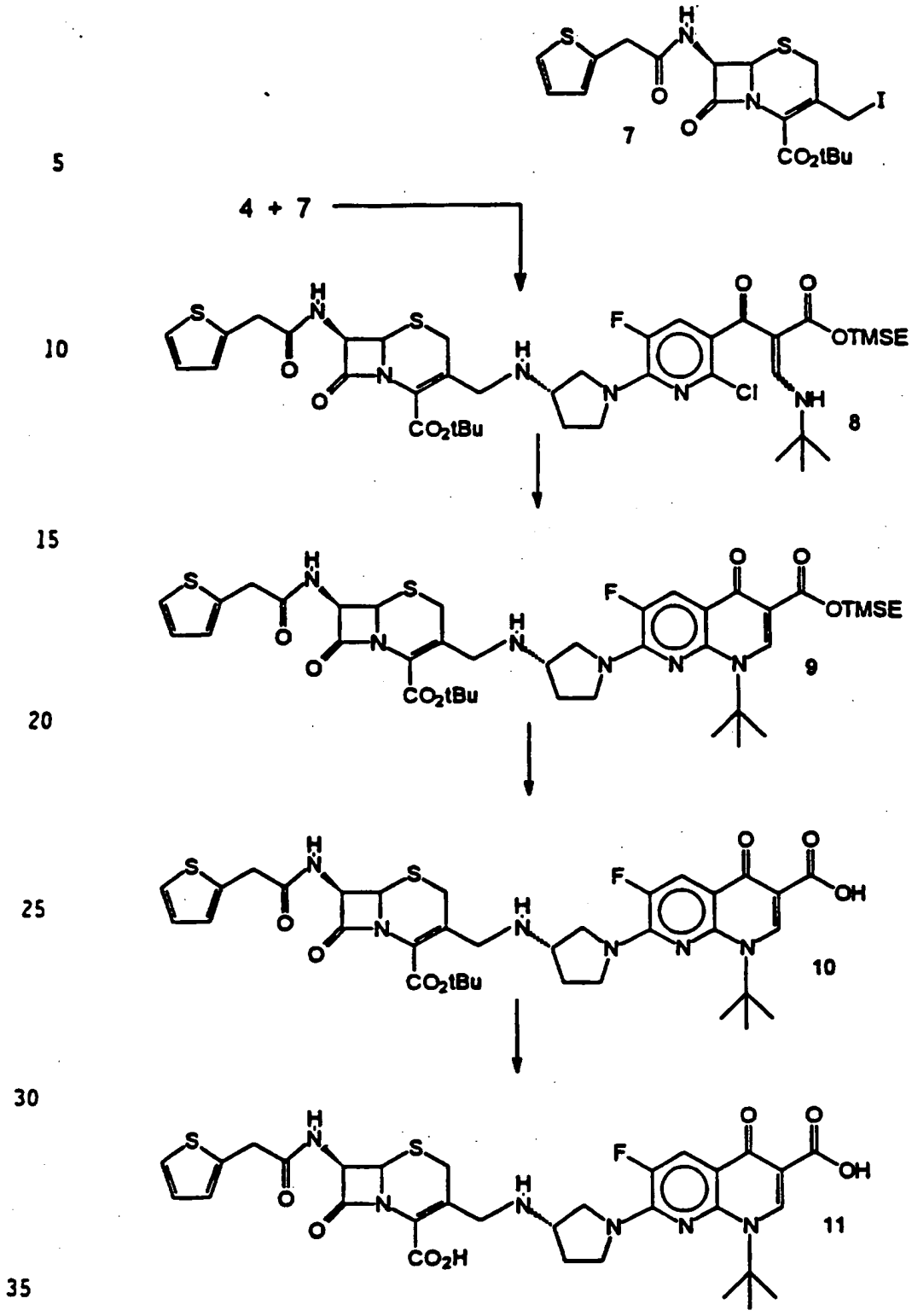








T a solution f 2-(trimethylsilyl)ethanol (33 mL) in toluene (80 mL) is added 4-dimethylaminopyridine (0.82 g), under N_2. Compound 1 (11.4 g) (prepared in the same manner as Comp und 3 in Example 8) is added and the

mixture is heated to reflux. Upon completion, the reaction mixture is cooled and saturated ammonium chloride (125 mL) is added, followed by the addition of EtOAc (150 mL). The layers are separated and the EtOAc portion is washed with water (4 x 50 mL) and brine (2 x 40 mL), and dried ($MgSO_4$). The solvents are removed in vacuo and the residue is subjected to column chromatography (silica) to provide Compound 2.

To a solution of Compound 2 (10.2 g) in triethylorthoformate (4.8 mL) is added acetic anhydride (15.4 mL). The mixture is fitted with a Dean-Stark trap and stirred at 130°C for 1.5 hours under N_2. The volatiles removed in vacuo and the residue is dissolved in CH_2Cl_2 (35 mL). The solution obtained is cooled t 0°C and tert-butylamine is added (2.6 mL). The reaction is stirred at 0°C for 5 minutes under N_2, allowed to warm to ambient temperature and stirred for 1 hour. The volatiles are removed in vacuo and the residue obtained is subjected to column chromatography (silica) to provide Compound 3.

To a cooled solution of Compound 3 (9.8 g) in anisole (60 mL) at 5-10°C is added TFA (60 mL). After stirring for 5 minutes under N_2, the ice bath is rem ved and the reaction is warmed to ambient temperature. After 2 hours, most f the TFA and some of the anisole is removed in vacuo. The residue is slurried in Et_2O (175 mL) and filtered. The solid is dissolved in a mixture of CH_2Cl_2 (110 mL) and saturated $NaHCO_3$ (75 mL) and stirred for 10 min. The CH_2Cl_2 porti n is separated, dried ($MgSO_4$), treated with activated charcoal, and evaporated in vacuo. The residue is crystallized with hexane to give Compound 4.

To a cooled (0°C) solution of tert-butyl 7-aminocephalosporanate (30 g) (Compound 5), prepared as described in R. J. Stedman, 9 J. Med. Chem. 444 (1966), which is incorporated by reference herein, in THF (1.5L) is added a solution of sodium bicarbonate (12.93 g) in water (1.5 L). To this mixture is added a solution of 2-thiopheneacetyl chloride (13.1 mL). The ice bath is removed and the reaction is stirred at room temperature until complete. The volatiles are removed in vacuo until an aqueous mixture is obtained. This mixture is extracted with EtOAc (4 x 500 mL) and the combined EtOAc layers are dried ($MgSO_4$). The EtOAc is removed in vacuo until approximately 200 mL of EtOAc remains. Hexane is added to this solution, until a precipitate begins to form. The mixture is then cooled to -20°C and held at this temperature for 16 hours. The resulting slurry is filtered and washed with hexanes to provide Compound 6.

To a solution of Compound 6 (10 g) in CH_2Cl_2 (150 mL) is slowly added iodotrimethylsilane (3.5 mL), under N_2. After stirring f r 30 minutes, additi nal iodotrimethylsilane (1.85 mL) is added and stirring is continued for 30 minutes m re. The reaction is quenched by slowly adding a cold 5% soluti n of sodium

thiosulfate (50 mL). The CH_2Cl_2 portion is washed with a cold 5% solution of sodium thiosulfate (50 mL), a cold solution of 5% $NaHCO_3$ (50 mL), cold water (50 mL) and brine (2 x 50 mL). The CH_2Cl_2 solution is dried and the volatiles are removed in vacuo until about one third of the solvent remains. The resulting solution is cooled and product crystallized by the addition of hexanes to provide Compound 7.

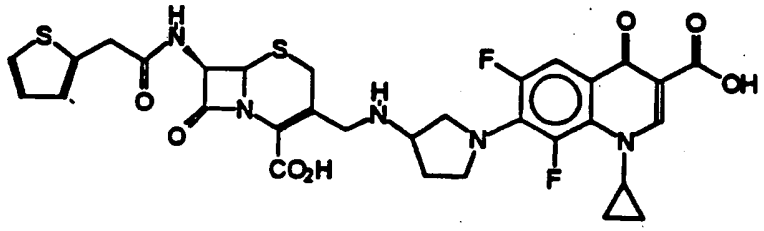
To a cooled (-40°C) solution of Compound 4 (2.26 g) in DMF (13 mL) and CH_2Cl_2 (13 mL) is added diisopropylethylamine (0.71 mL) is added, under N_2. After stirring for 30 minutes, a solution of Compound 7 (2.1 g) in DMF (13 mL) and CH_2Cl_2 (13 mL) is slowly added. The mixture is stirred for 1 hour at -40°C and then stirred at 0°C for 1 hour, and allowed to warm to ambient temperature. Upon completion, the reaction is diluted with CH_2Cl_2 (100 mL) and washed with cold 1M HCl (2 x 80 mL) and cold brine (2 x 80 mL). The organic portion is separated and the solvents are removed in vacuo to provide a residue that is subjected to column chromatography (silica) to provide Compound 8.

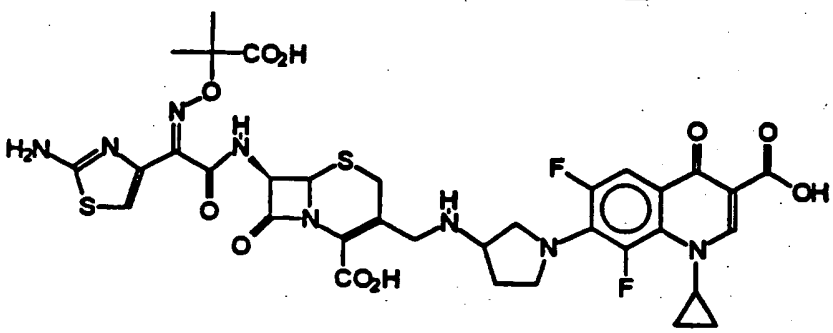
To a solution of Compound 8 (3.45 g) in CH_3CN (40 mL) is added N,O-bis(trimethylsilyl)acetamide (3.56 mL). The reaction mixture is stirred under N_2 at ambient temperature until complete. The reaction is quenched with water (40 mL), and the resulting slurry is filtered and washed with a mixture of water and CH_3CN (5:1) to provide Compound 9.

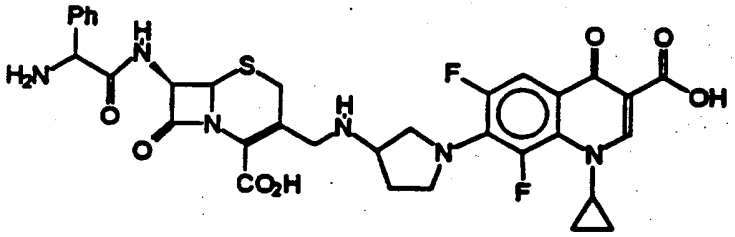
To a cooled (0°C) solution of Compound 9 (2.7 g) in THF (50 mL) is added a solution of tetra-n-butyl ammonium fluoride (10.4 mL of a 1M solution in THF), under N_2. The mixture is stirred at 0°C for 30 minutes and then warmed to ambient temperature. Upon completion, hexamethyldisiloxane (2.27 mL) is added and the mixture is stirred for an additional 30 minutes. The volatiles are removed in vacuo to provide a residue which is crystallized by the addition of ether to provide Compound 10.

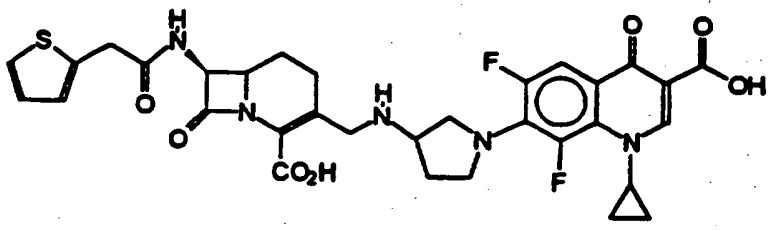
To a cooled (-15°C) solution of Compound 10 (1.6 g) and triethylsilane (1.22 mL) in CH_2Cl_2 (30 mL) is slowly added trifluoroacetic acid (33 mL), under N_2. After 30 minutes at -15°C, the mixture is allowed to warm to ambient temperature. Upon completion, the mixture is cooled to 0°C and is crystallized by the addition of cold ether to provide Compound 11.

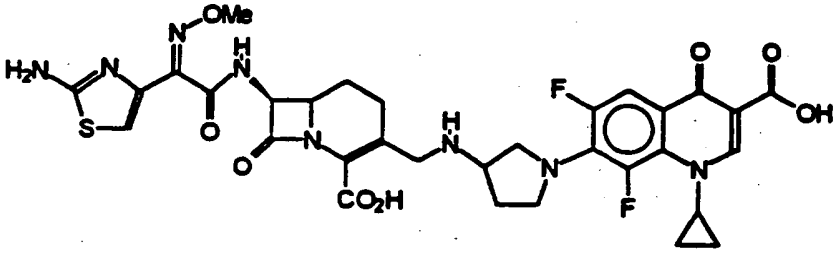
The following compounds are prepared according to Examples 8 and 9, with substantially similar results.

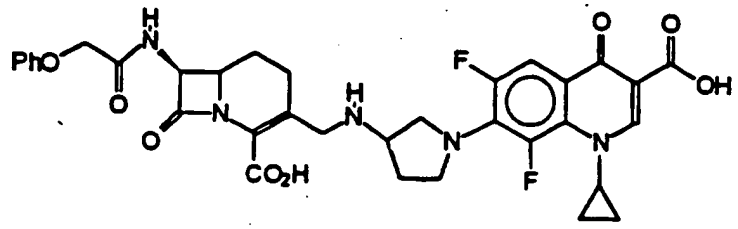


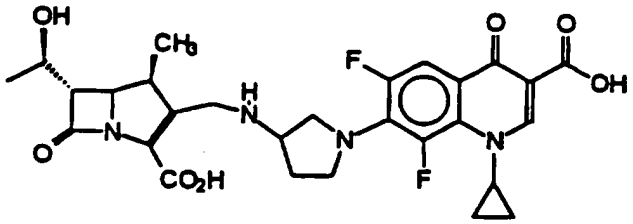


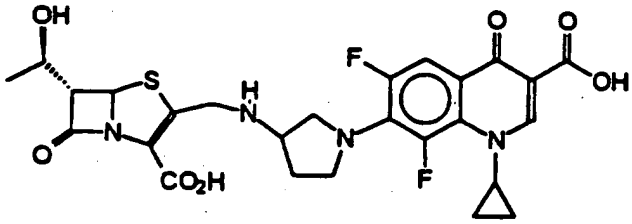


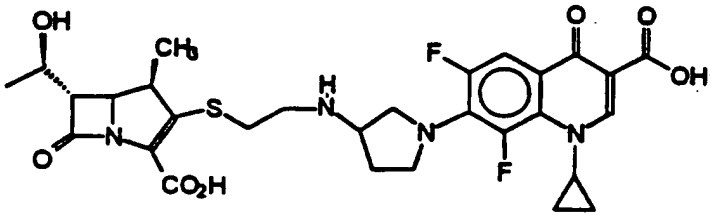


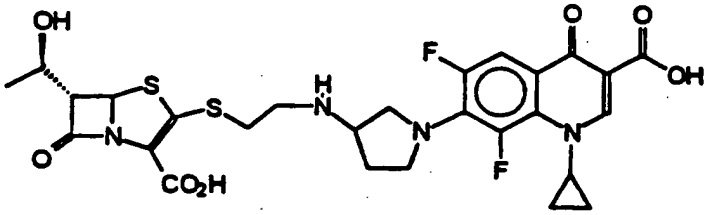


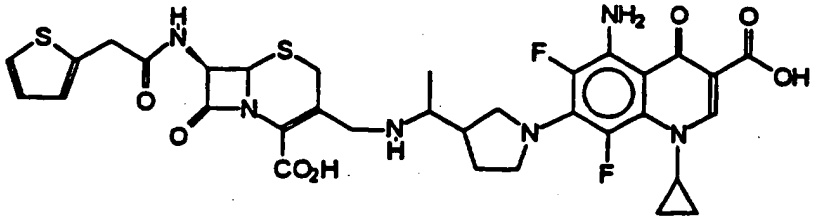


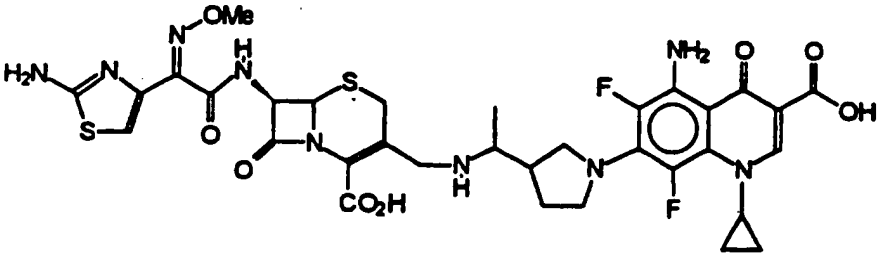


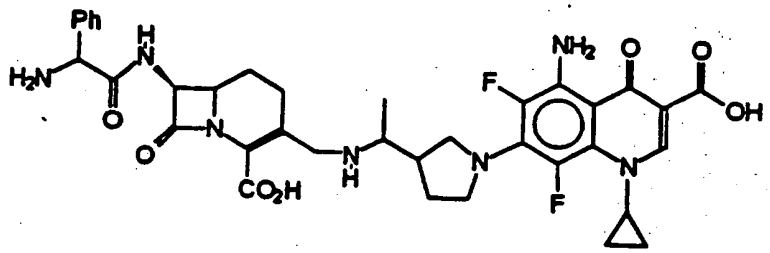


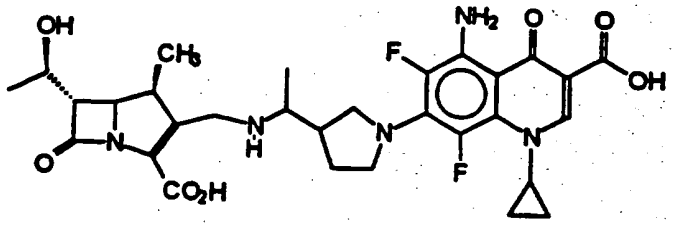


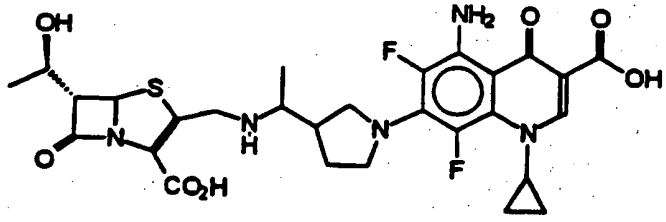


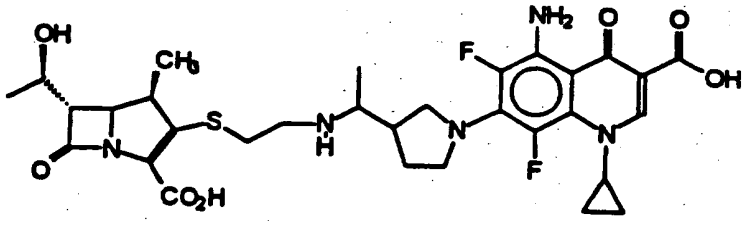


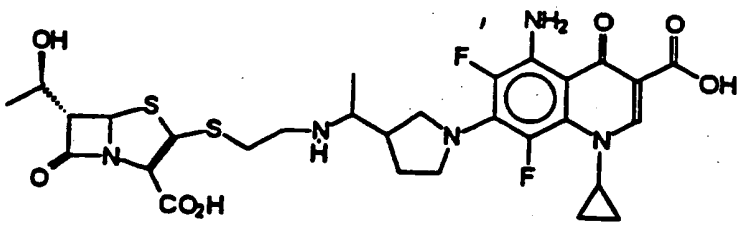


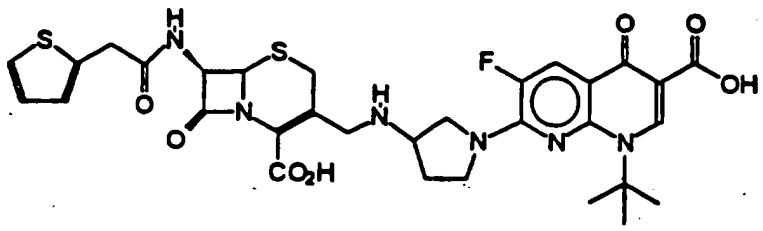


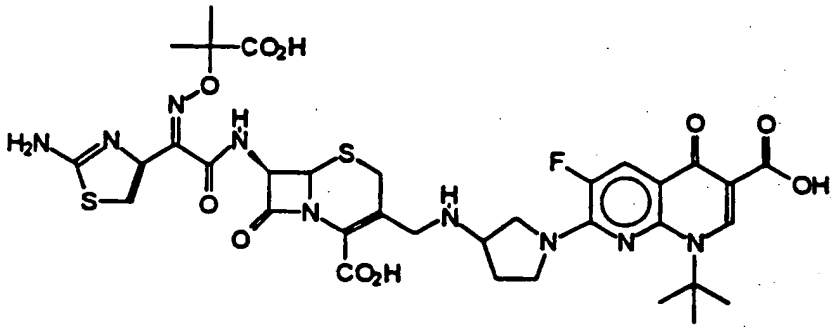


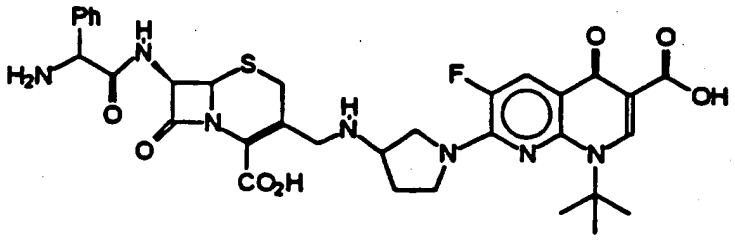


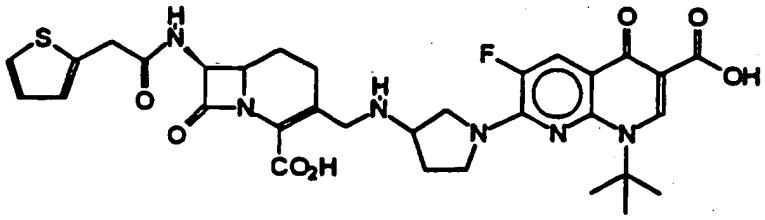


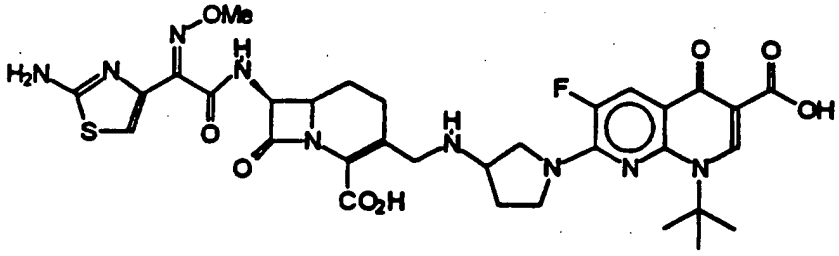


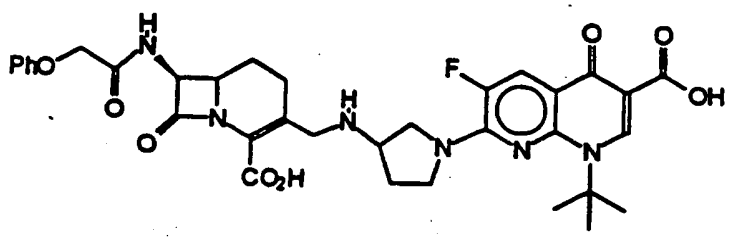


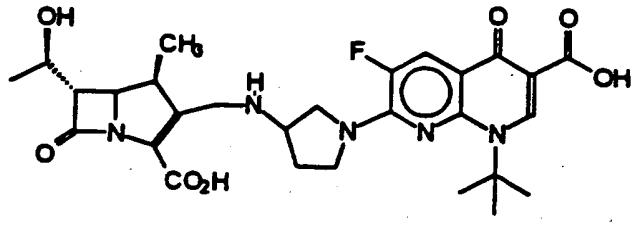


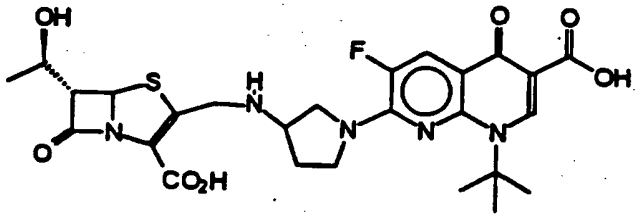


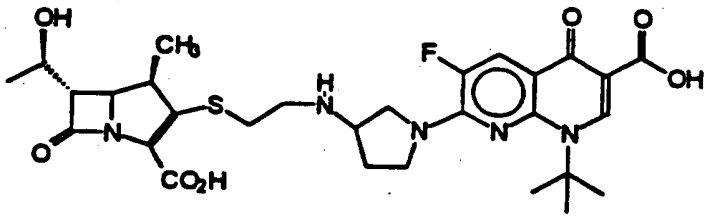


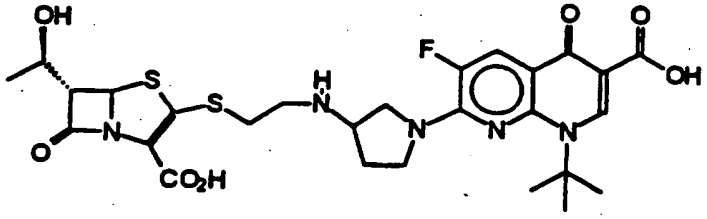


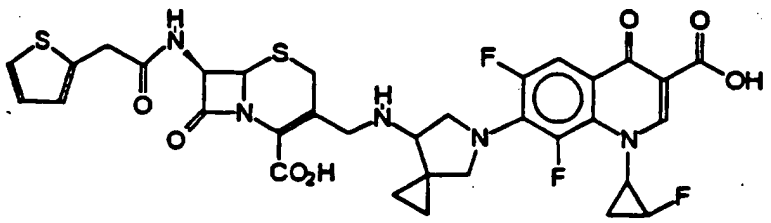


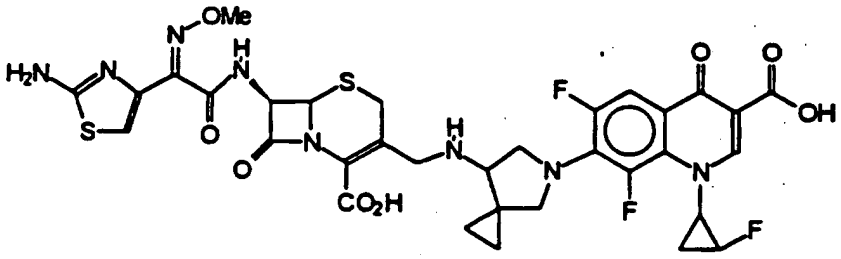


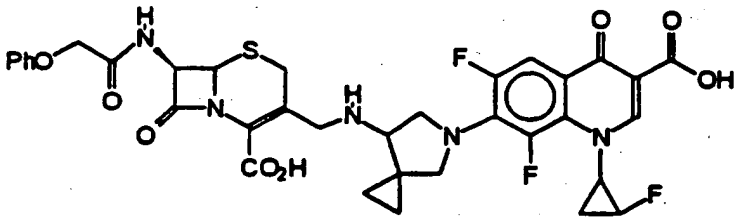


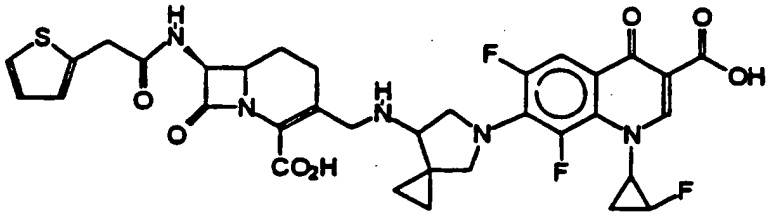


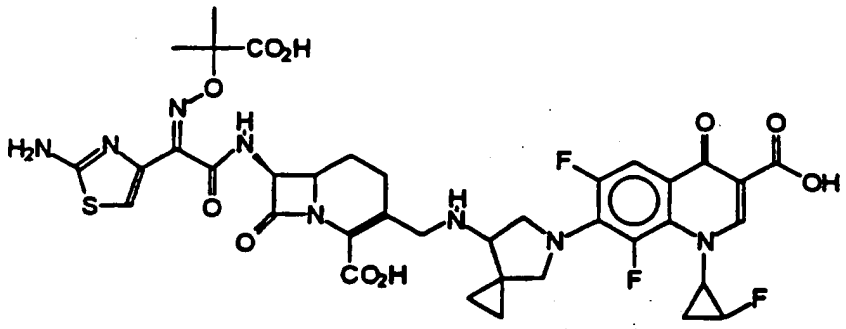


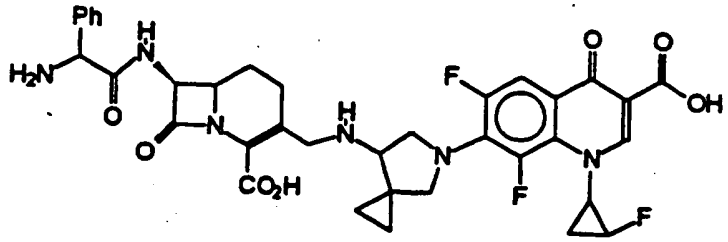


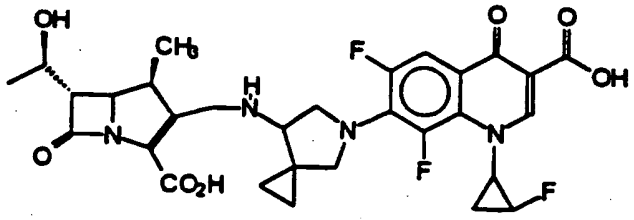


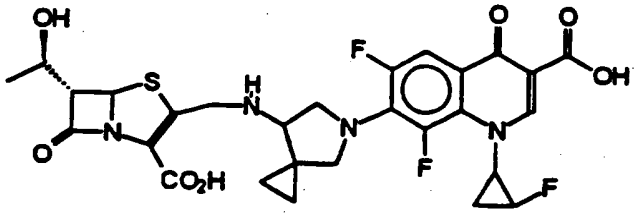


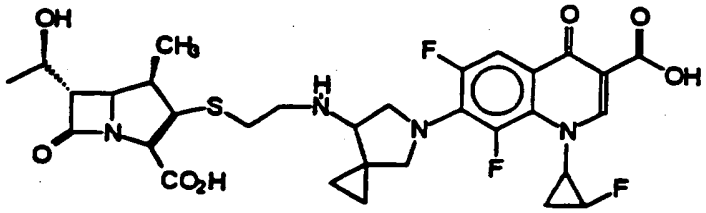


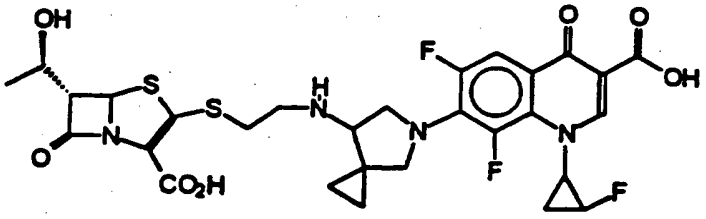


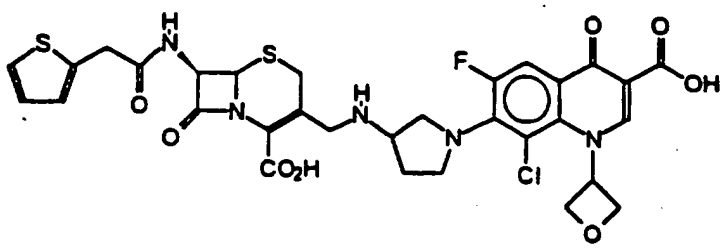


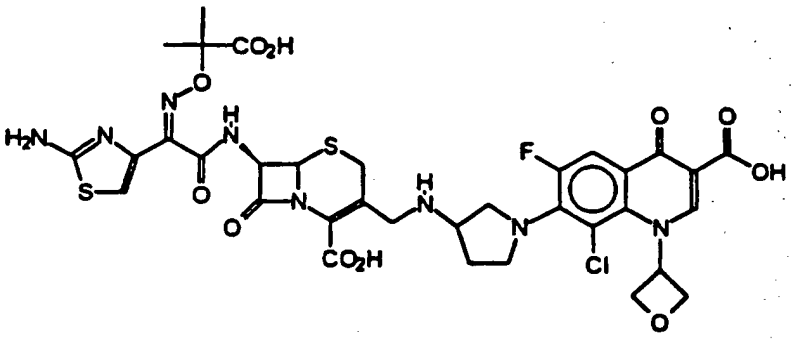


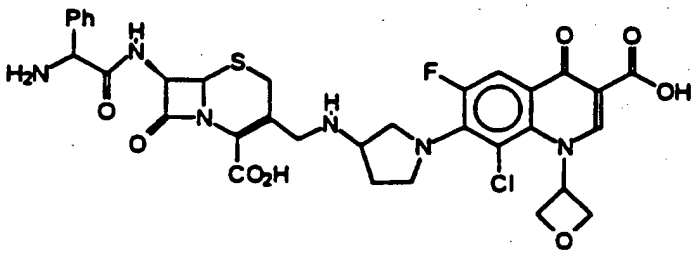


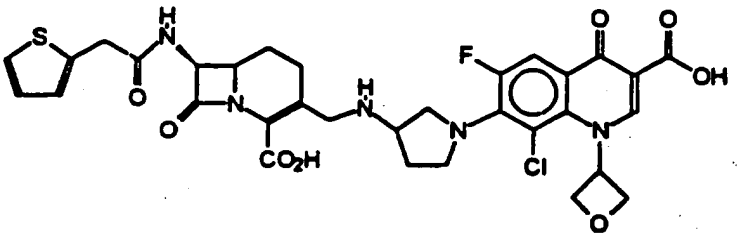


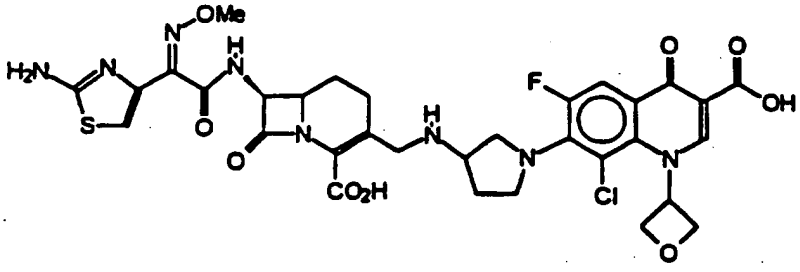


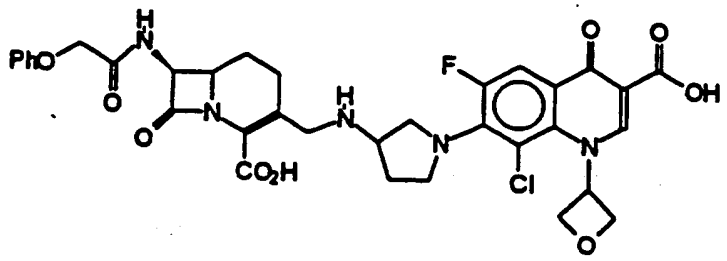


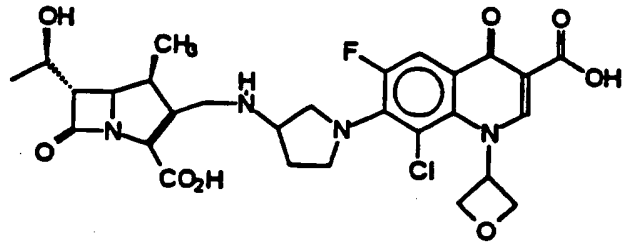


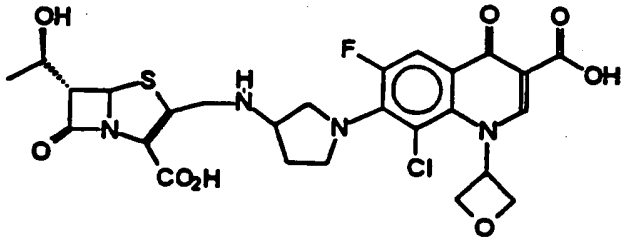


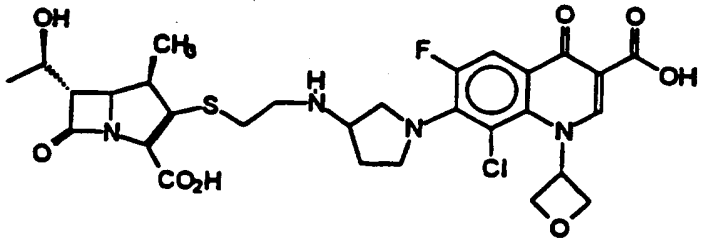


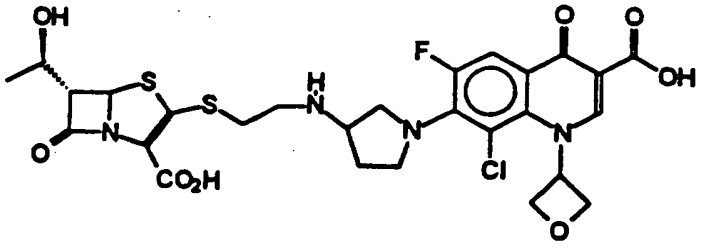


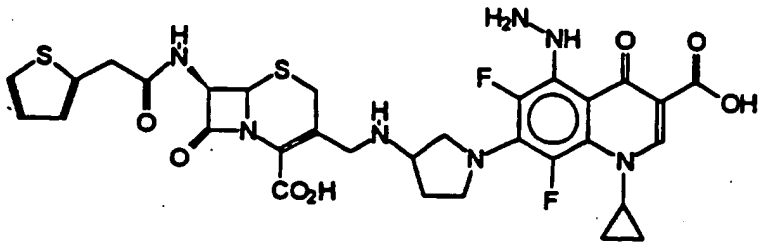


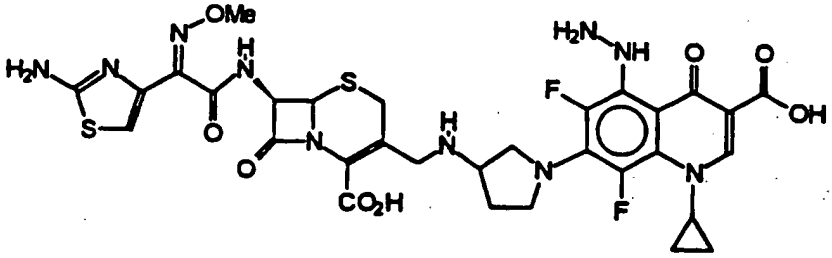


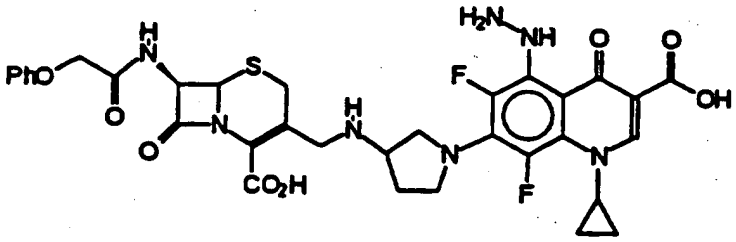


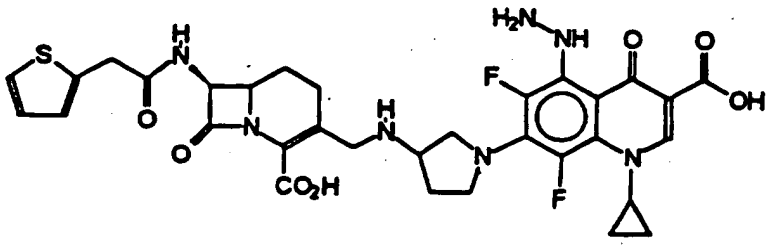


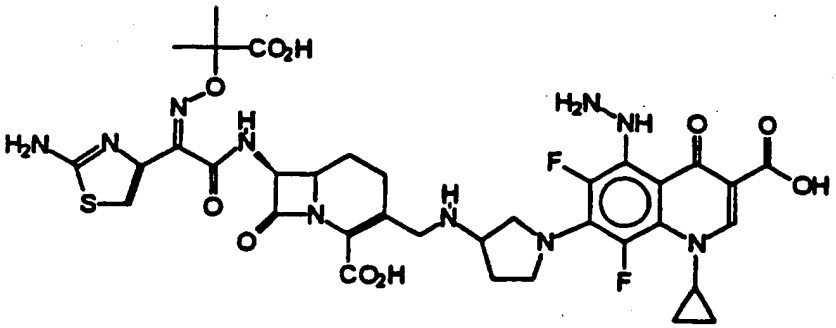


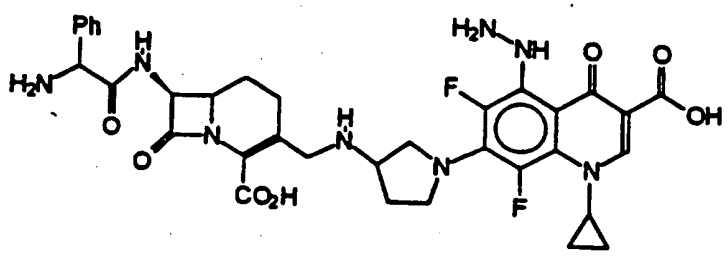


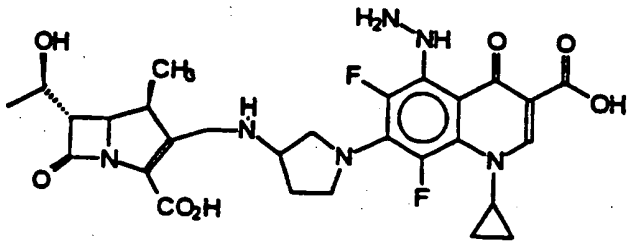


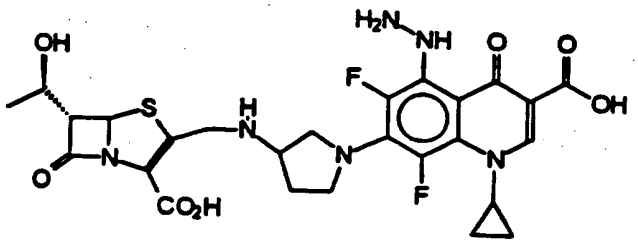


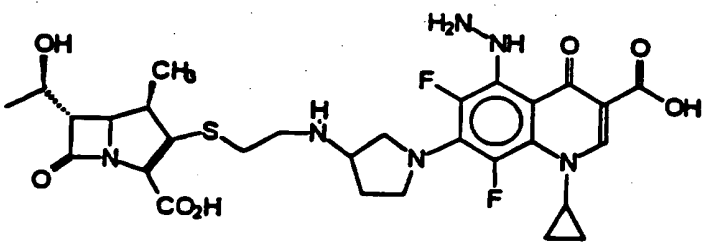


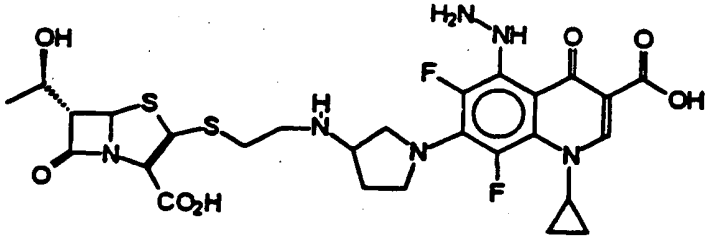


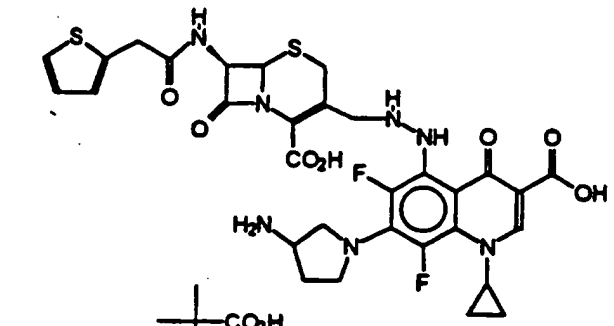


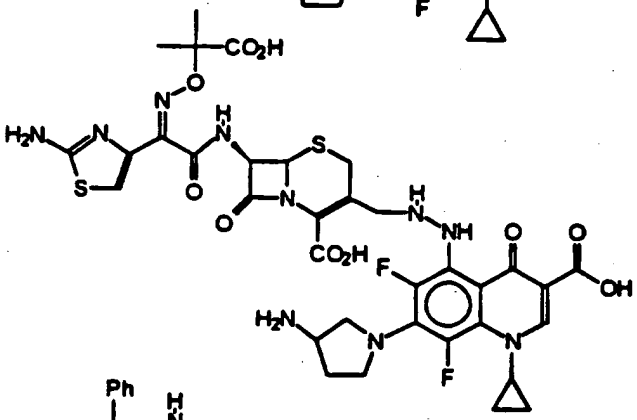


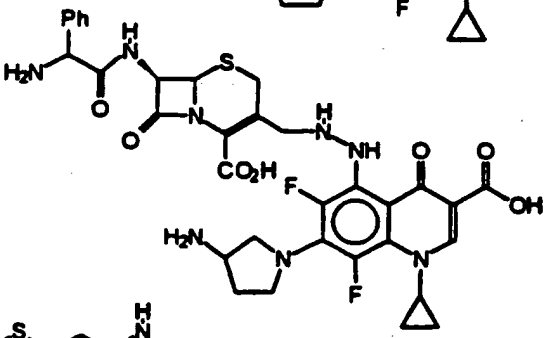


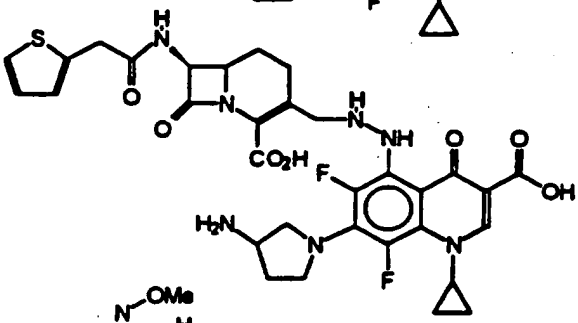


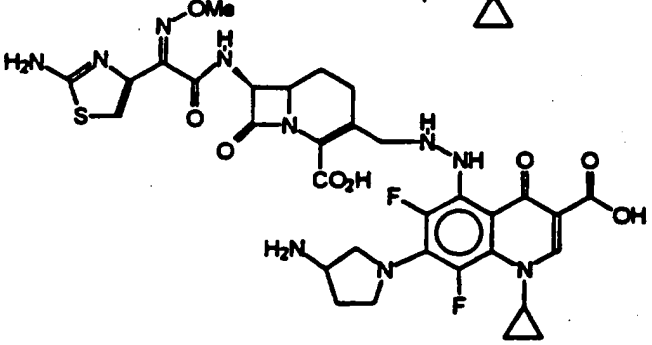


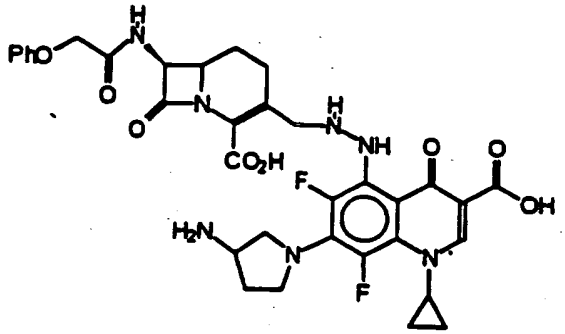


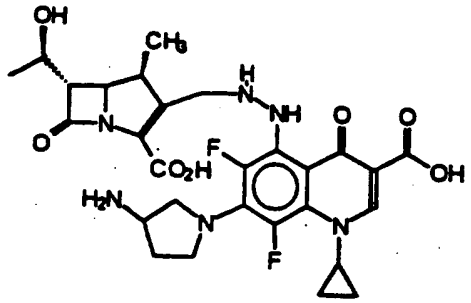


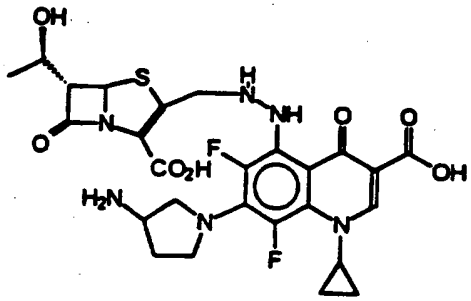


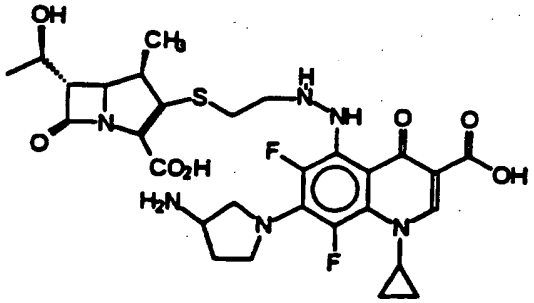


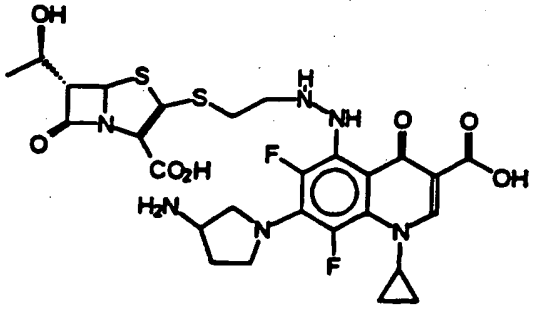


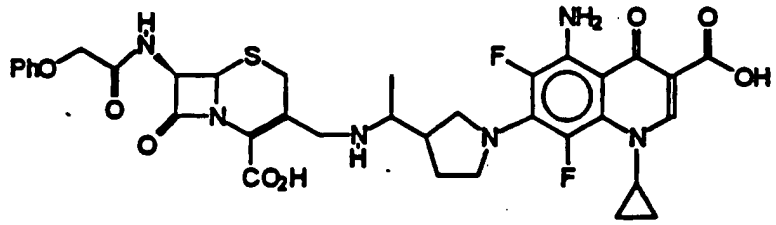


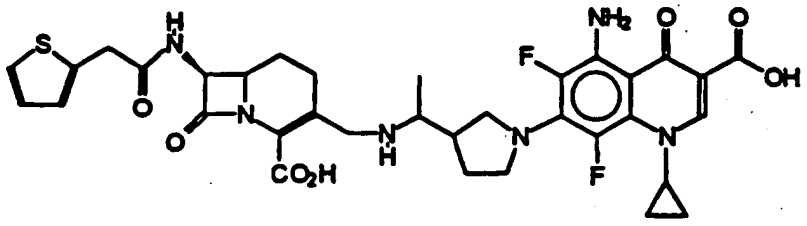


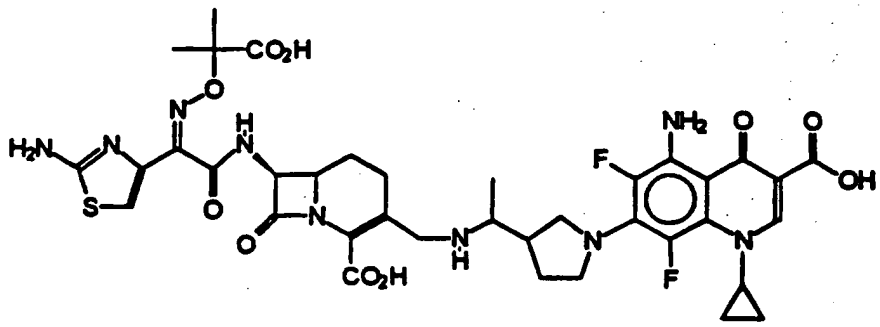




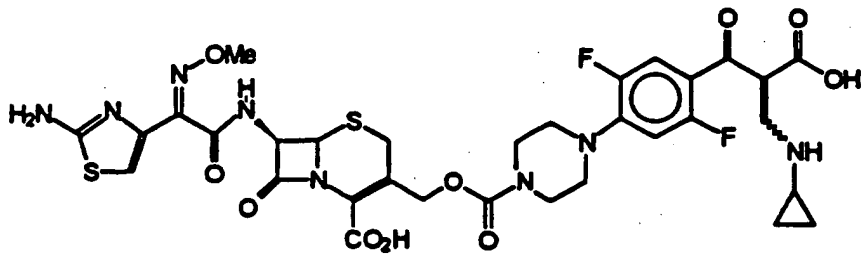


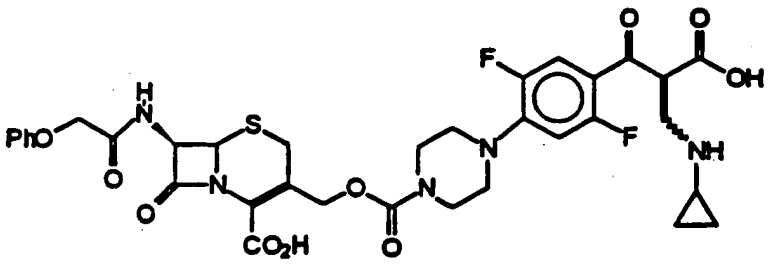


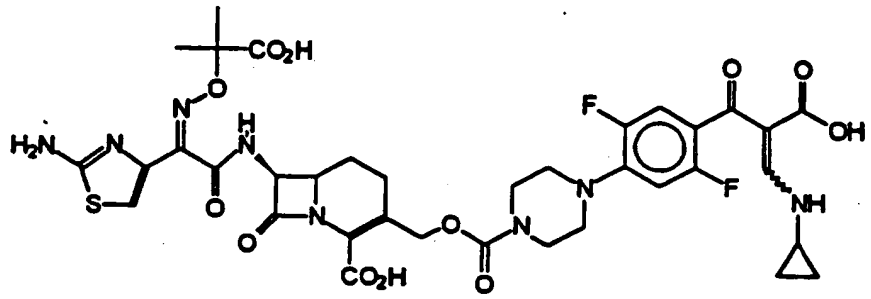


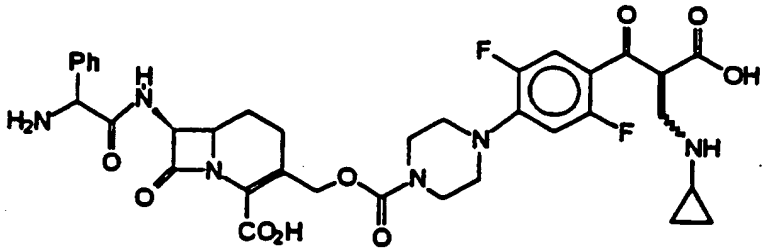


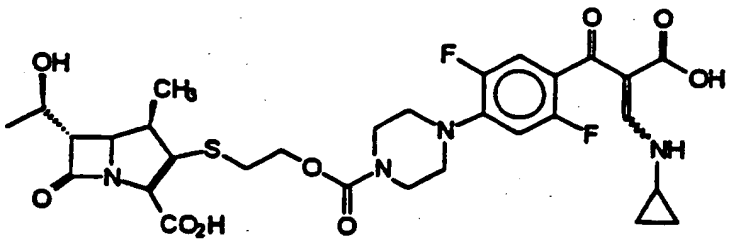
The following are examples of the novel intermediates of the present in invention. While illustrated in the acid form, those skilled in the art will recognize that the intermediates are preferably in a protected form.

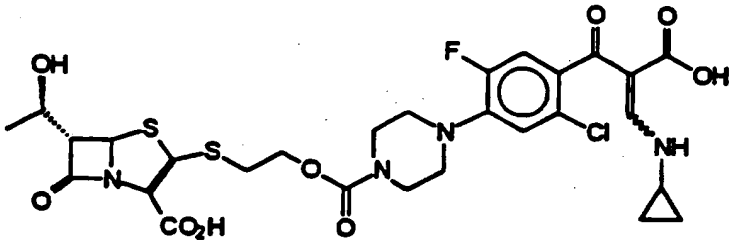


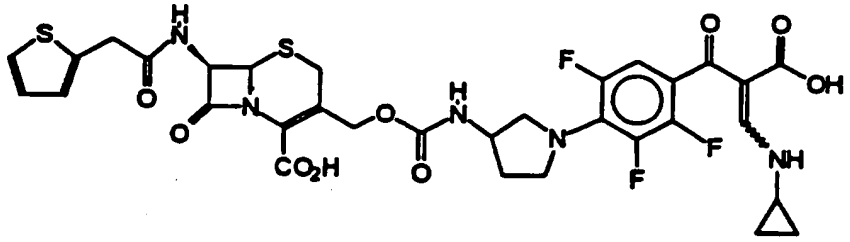


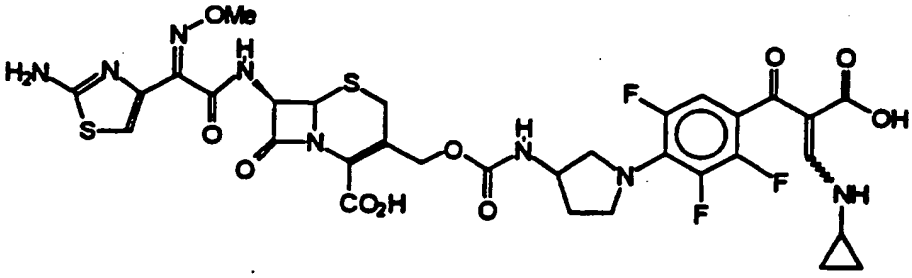


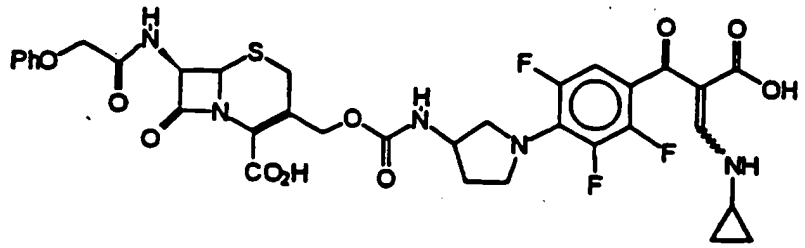


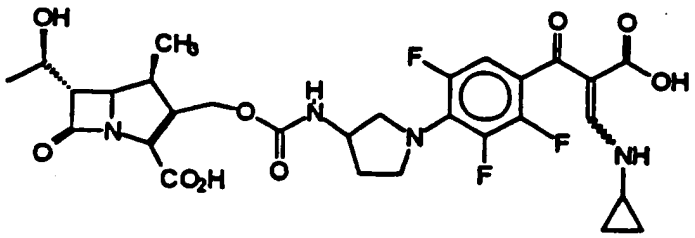


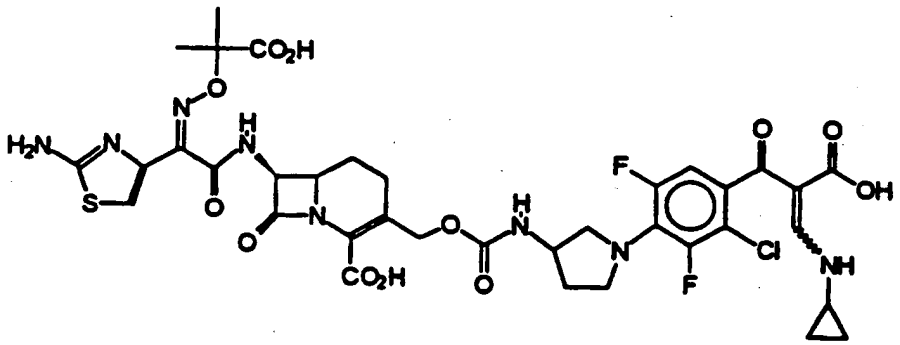


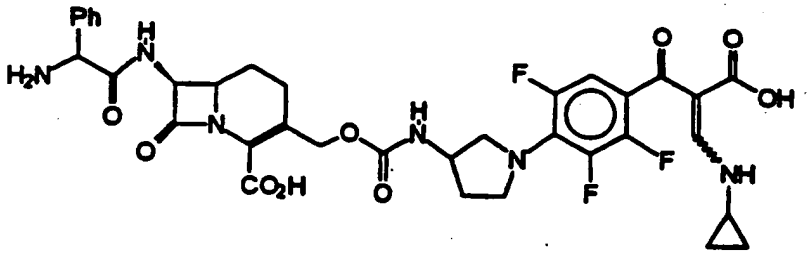


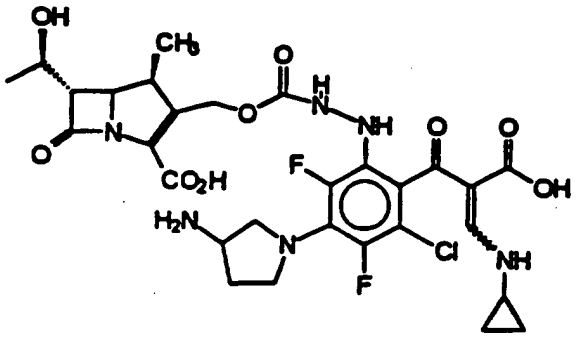


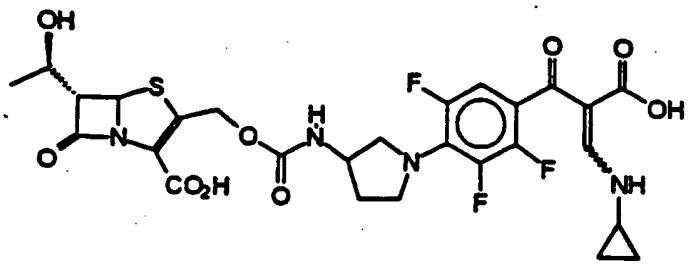


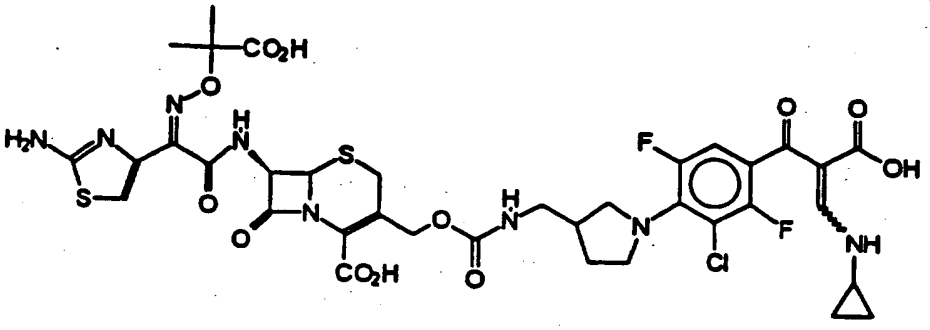


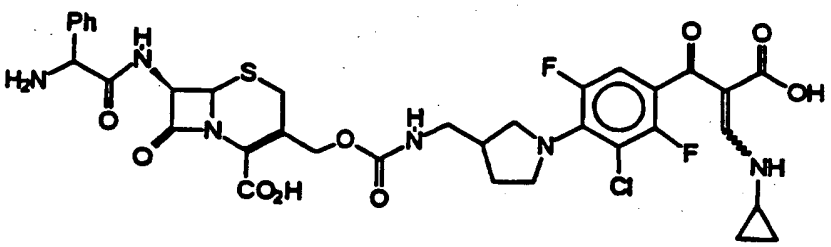


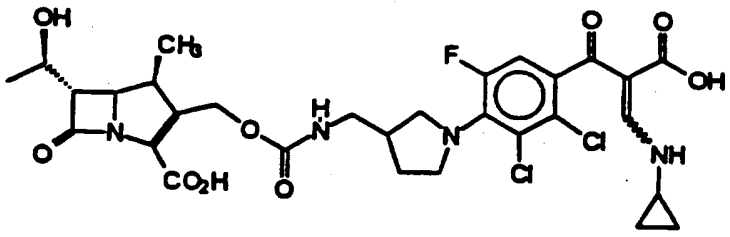


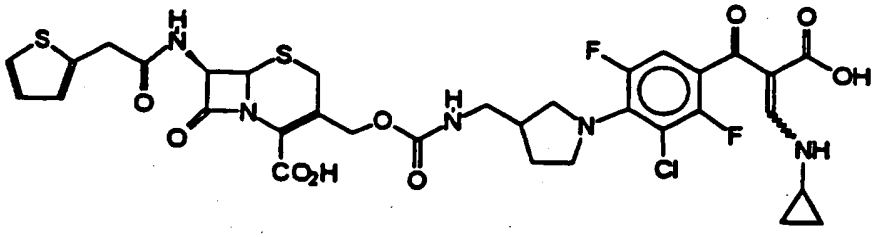


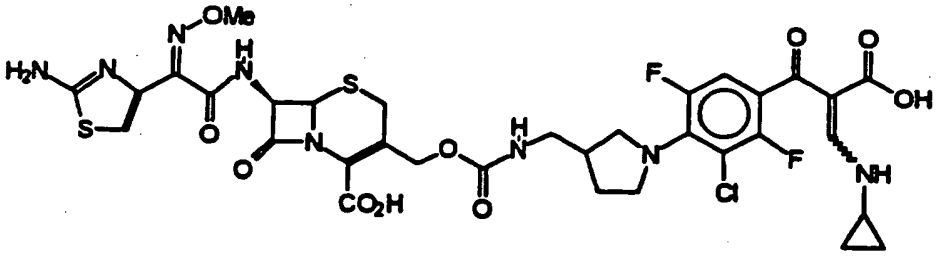


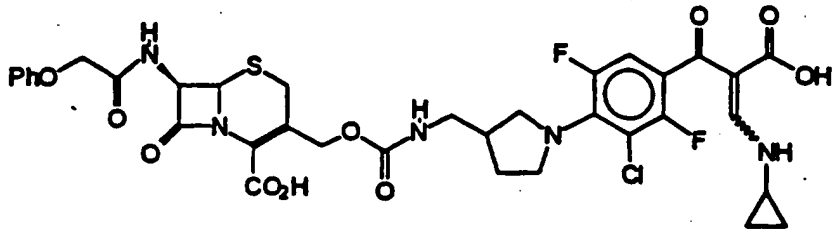


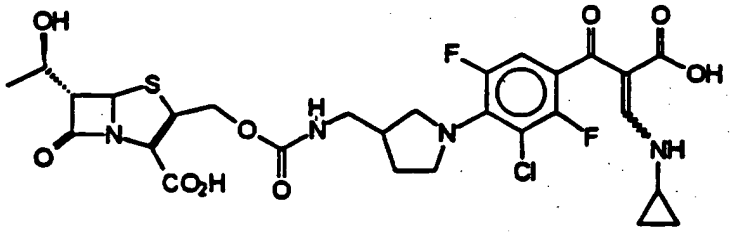


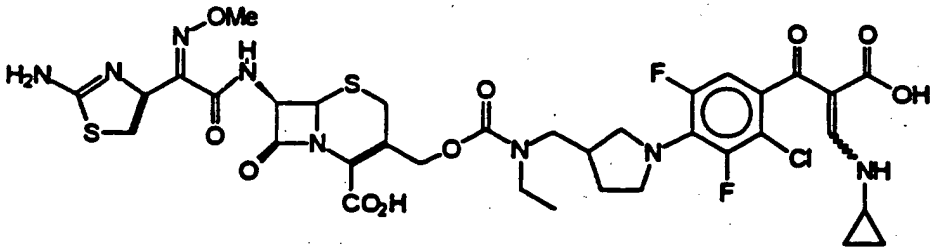


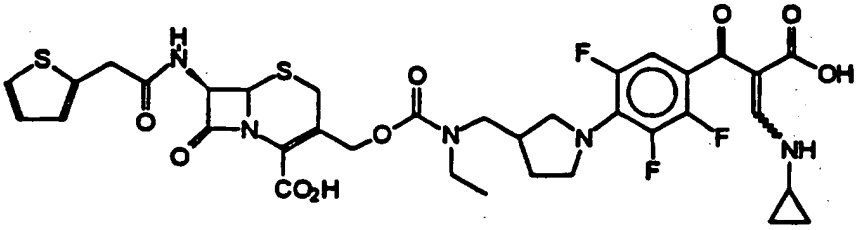


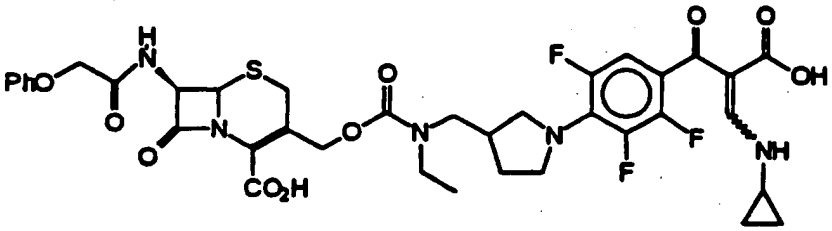


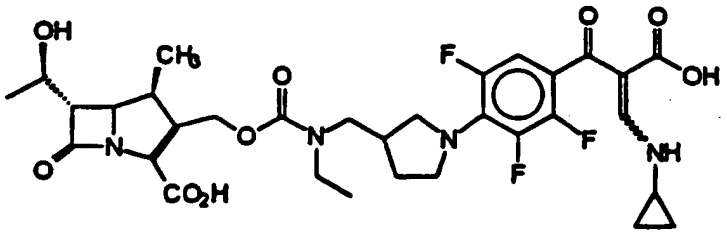


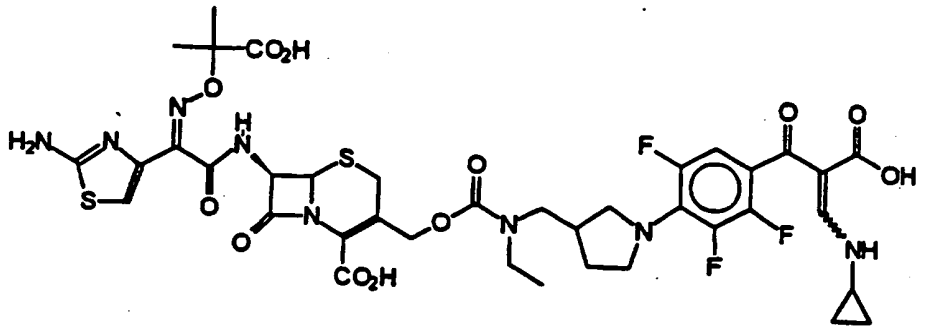


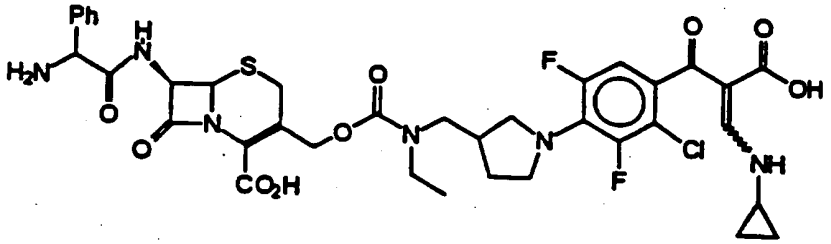


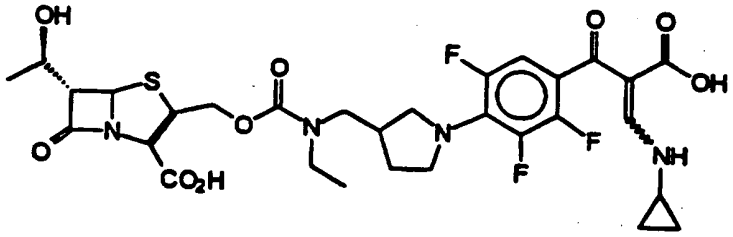


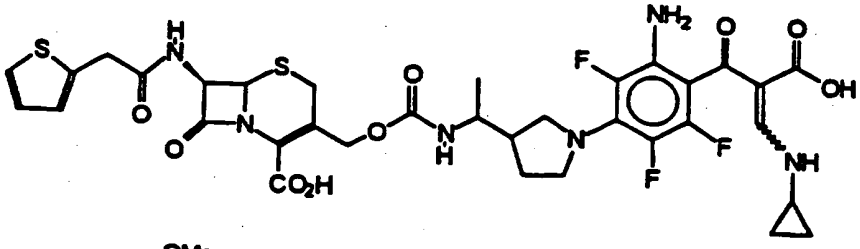


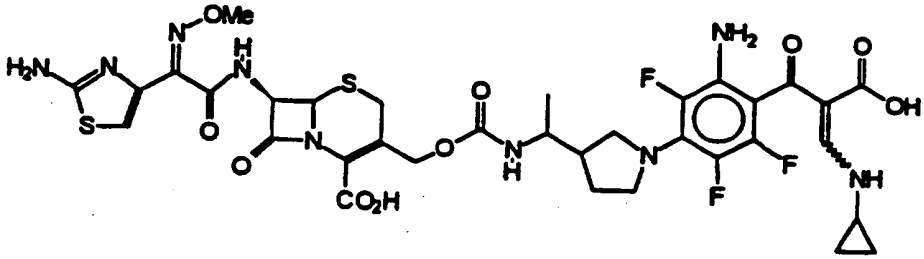


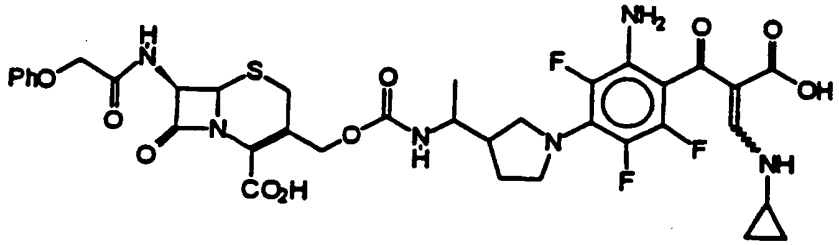


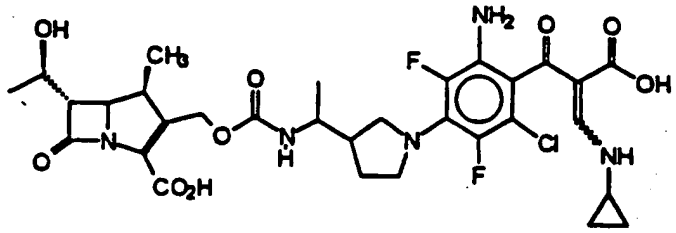


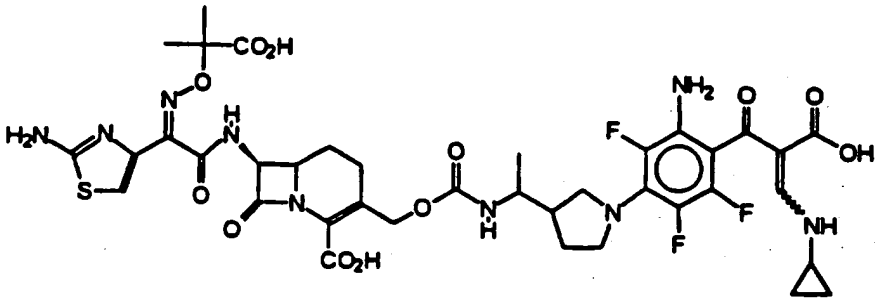


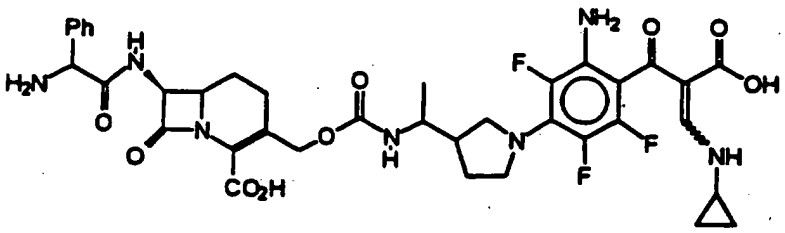


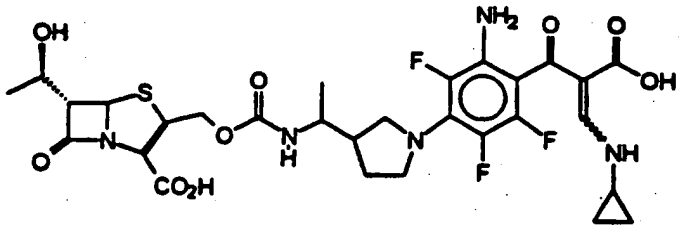


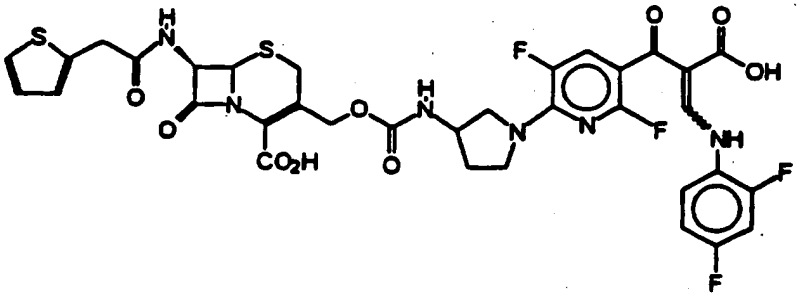


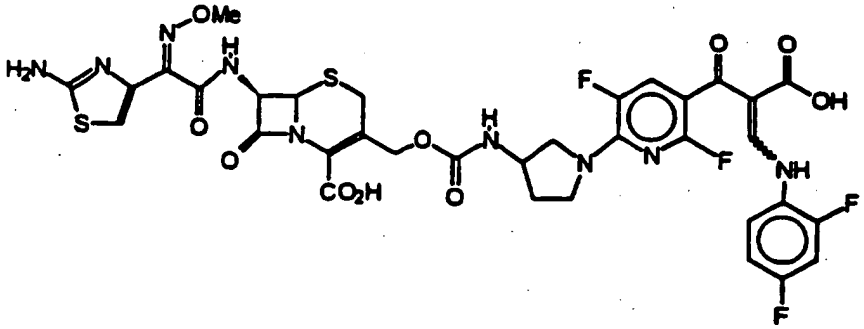


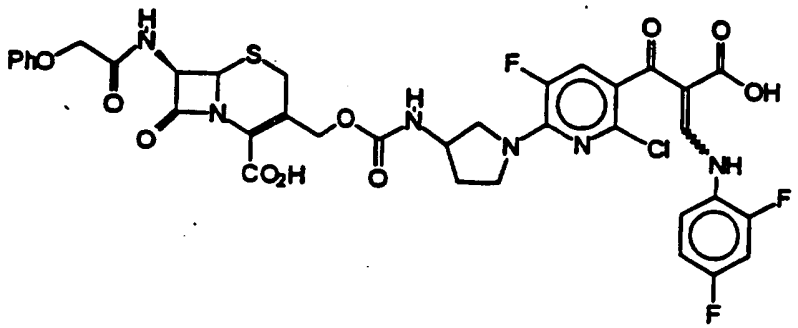


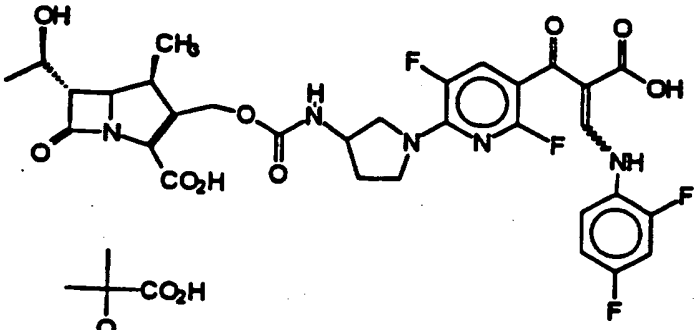


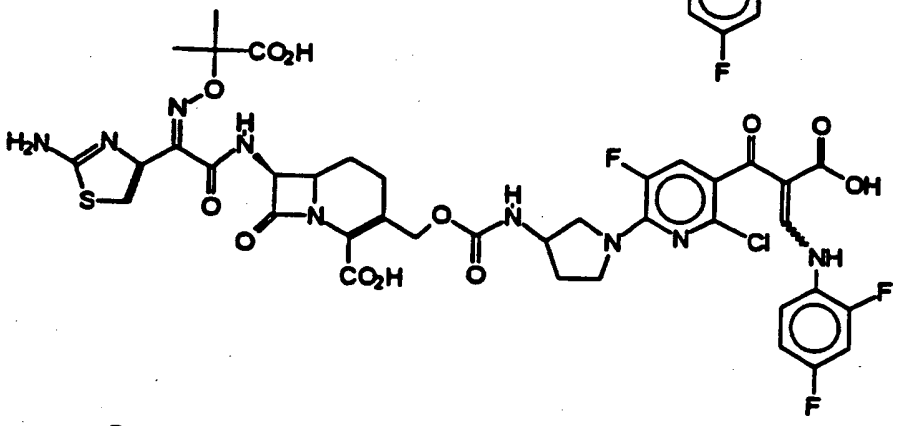


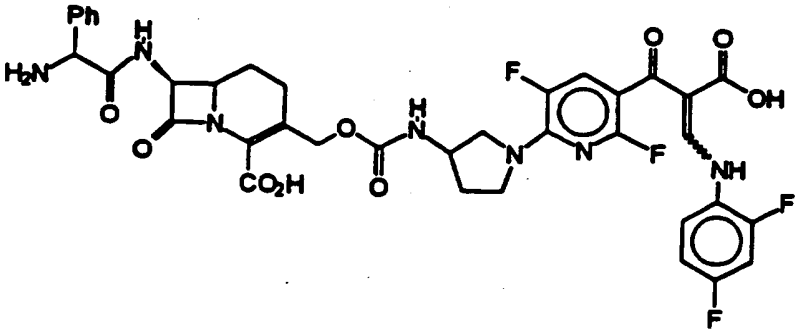


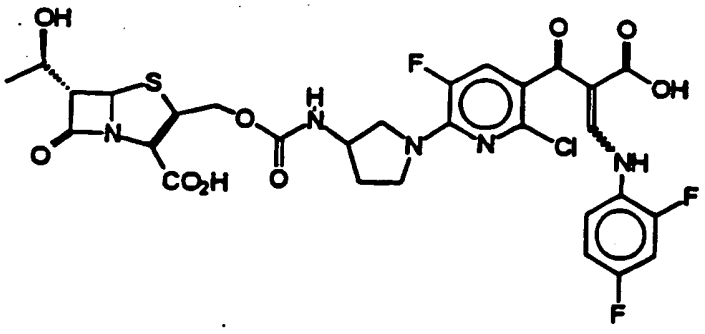


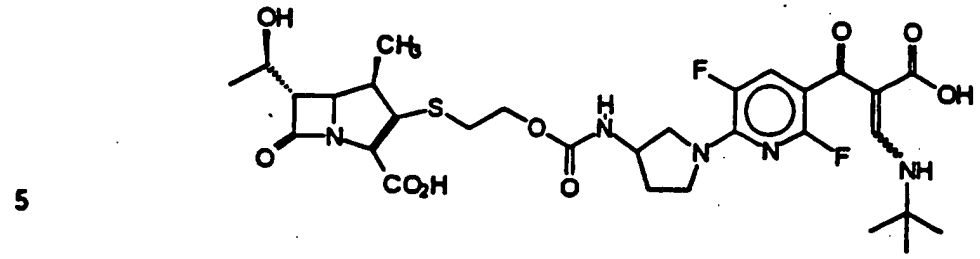


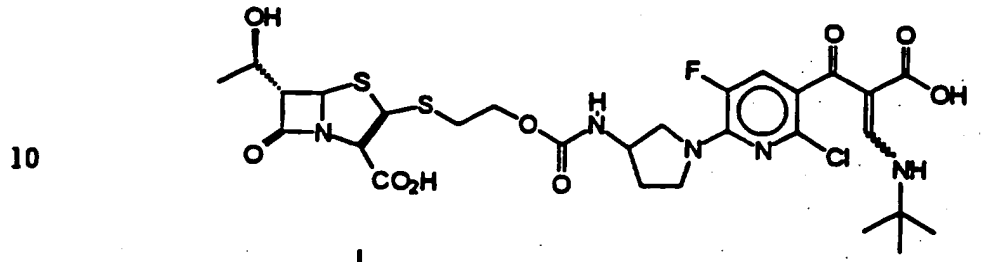


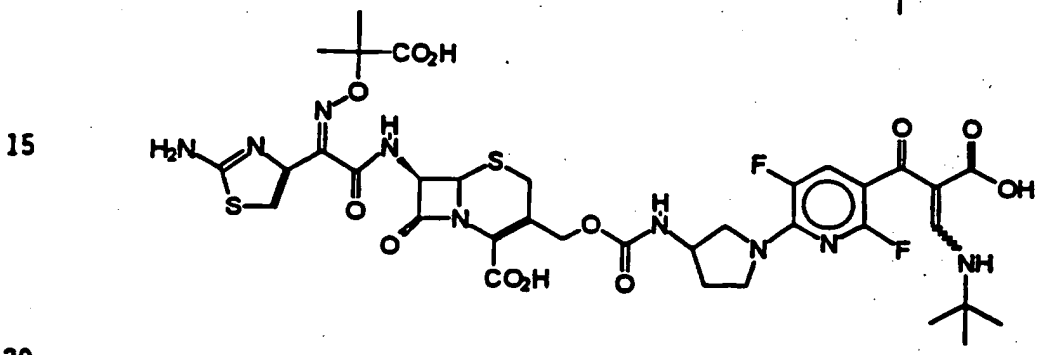


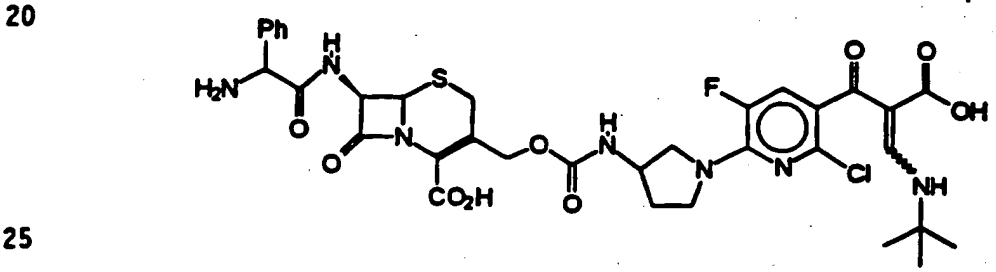


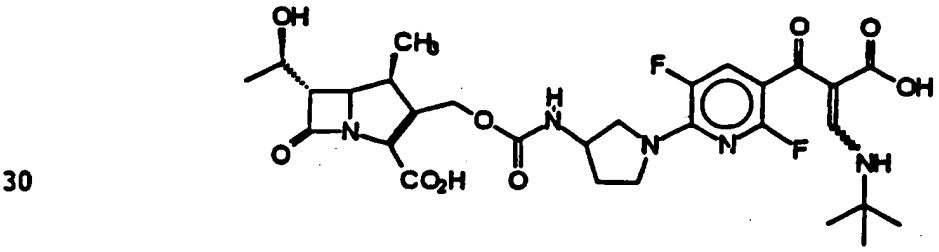


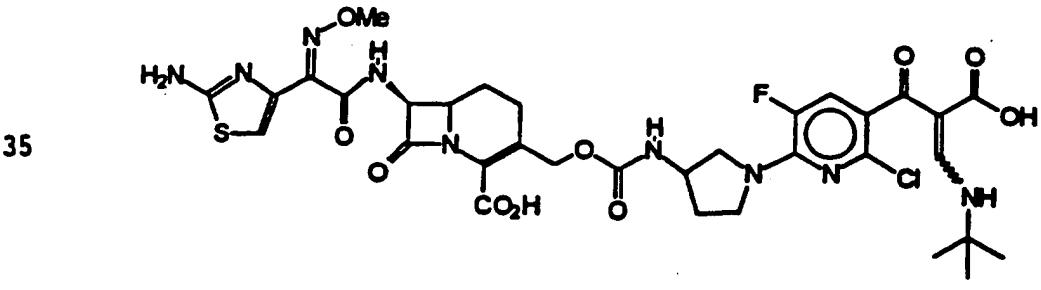


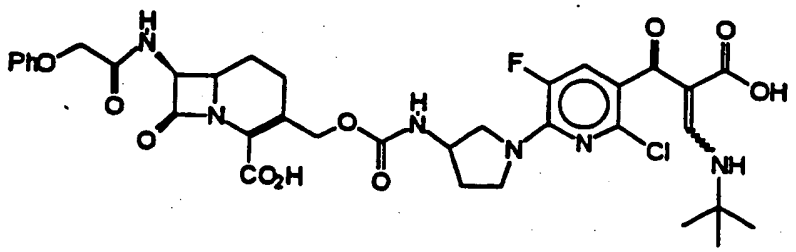


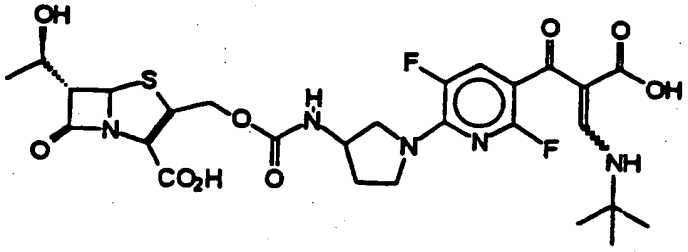


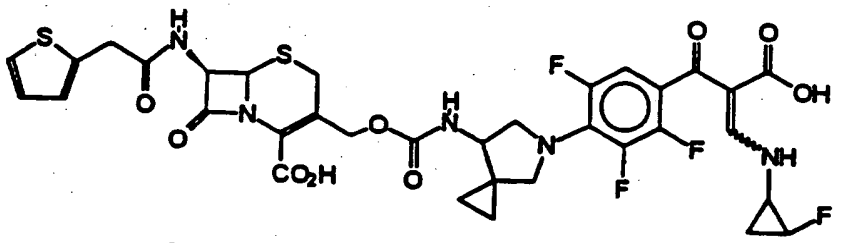


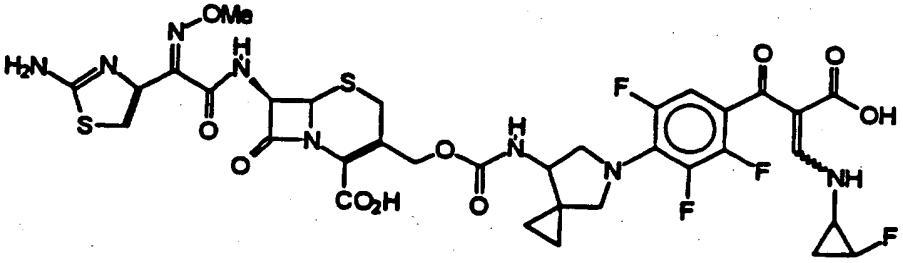


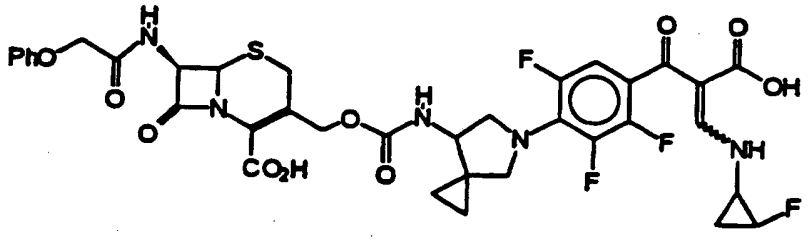


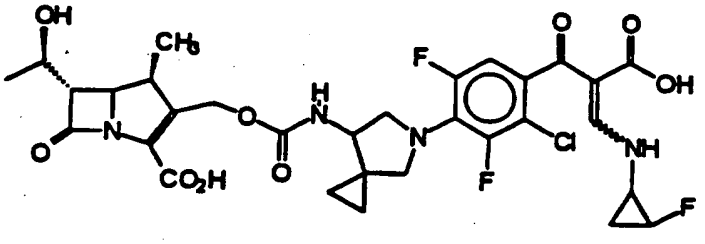


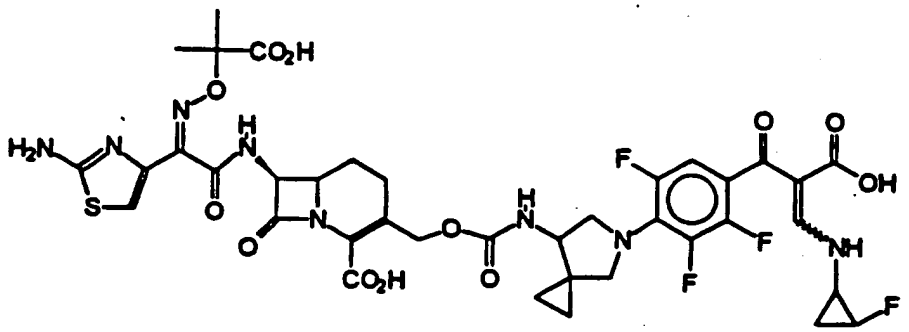


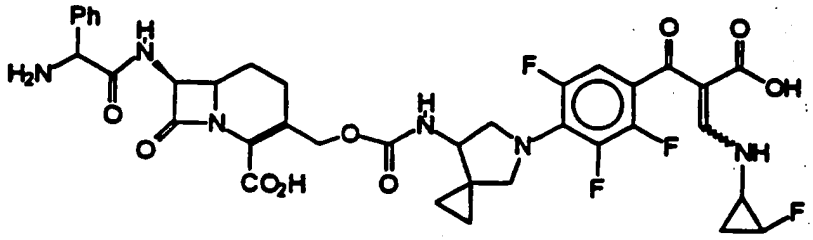


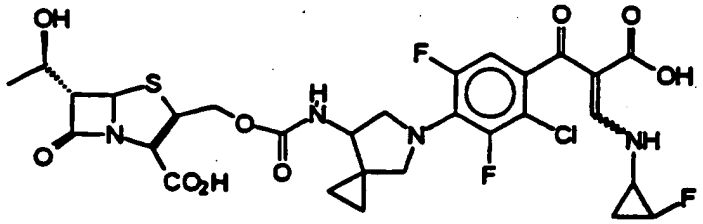


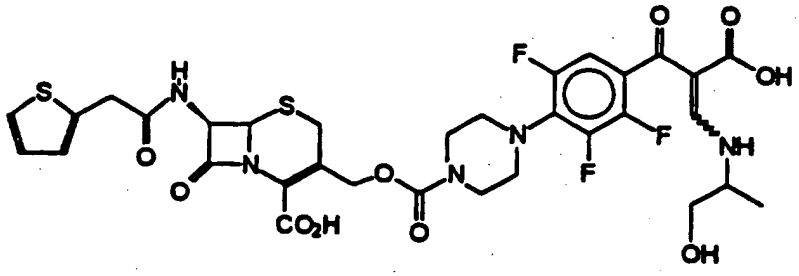


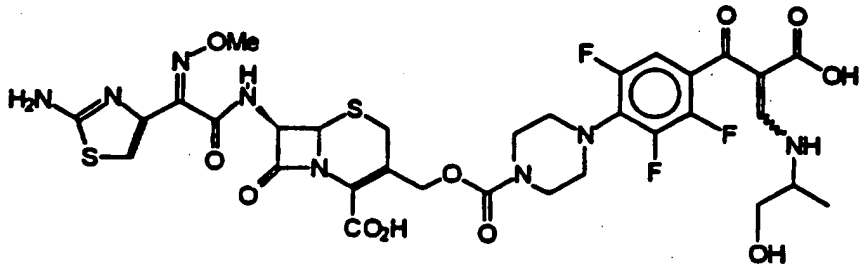


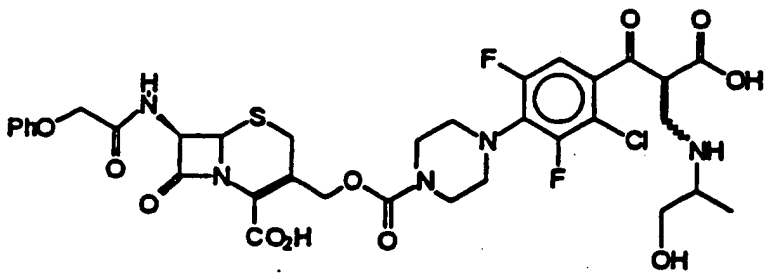


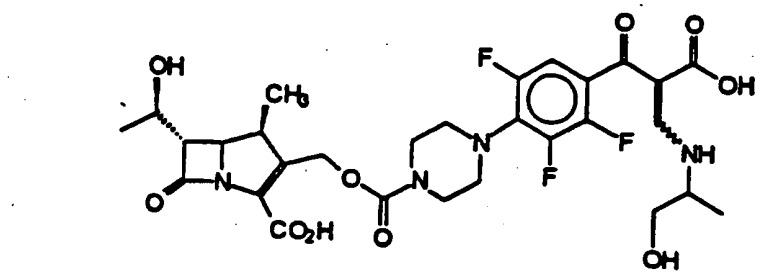


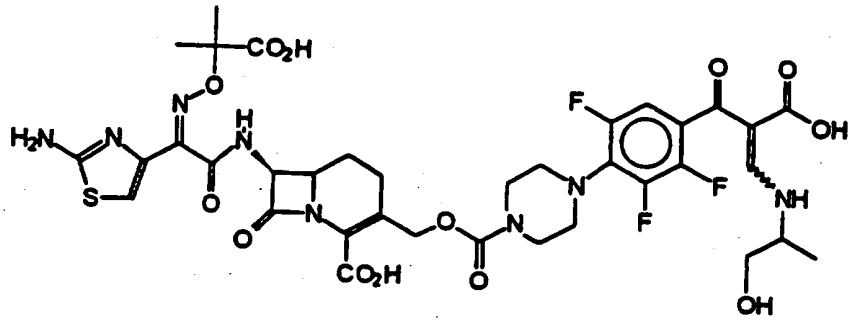


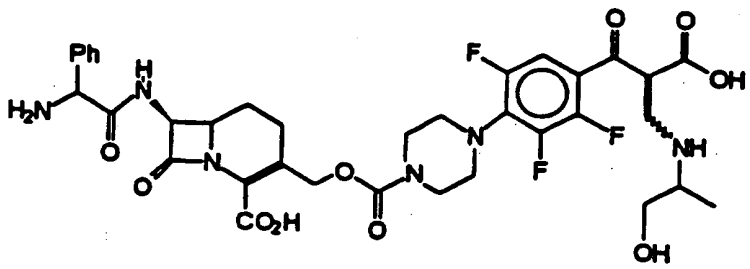


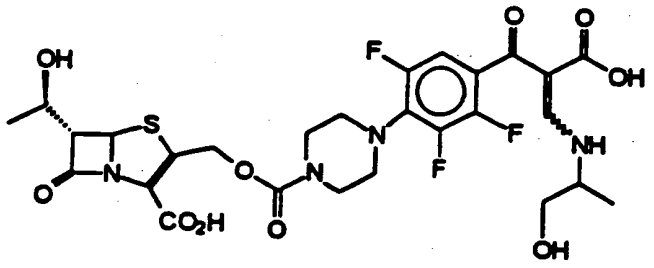


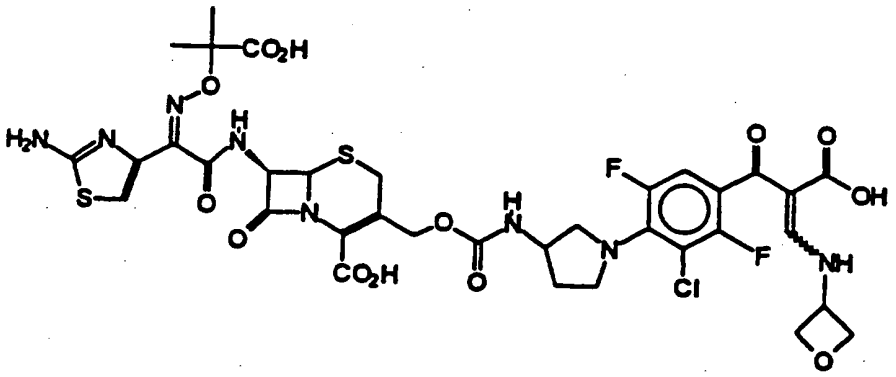


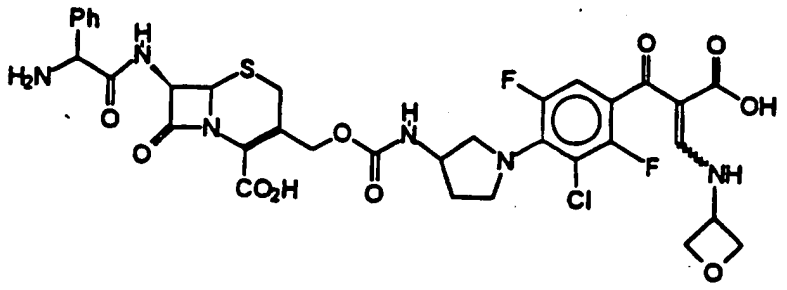


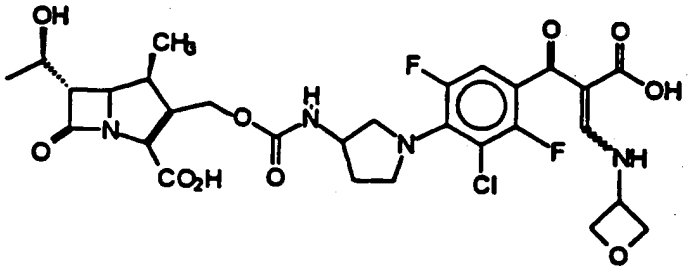


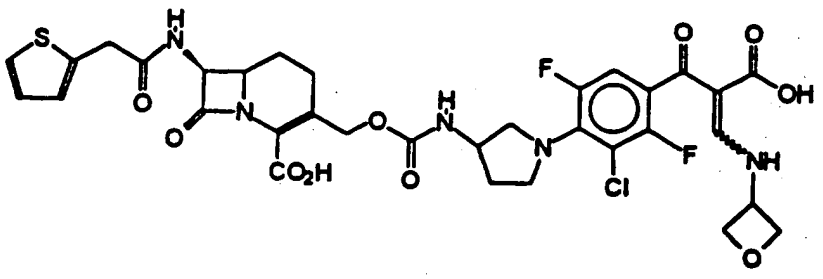


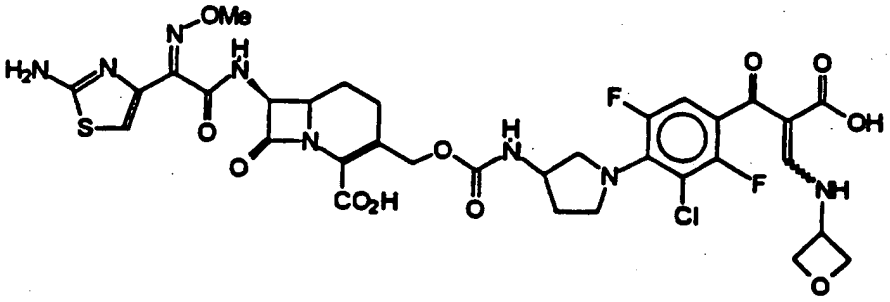


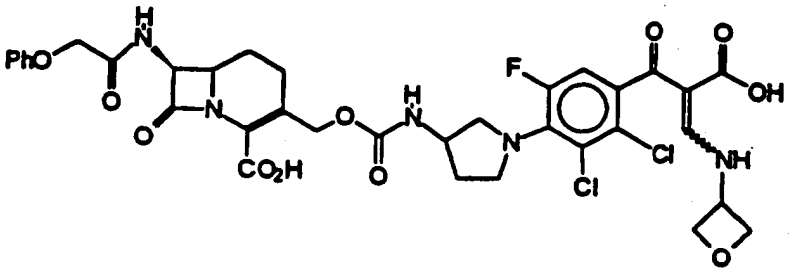


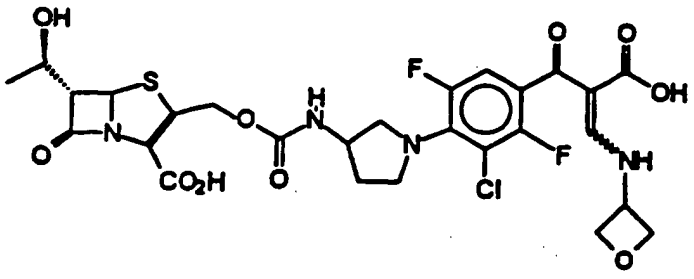


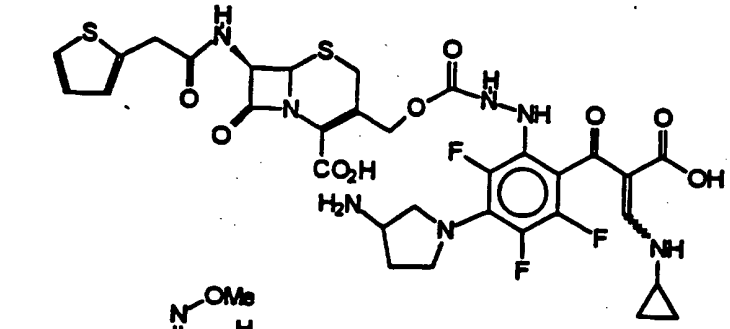


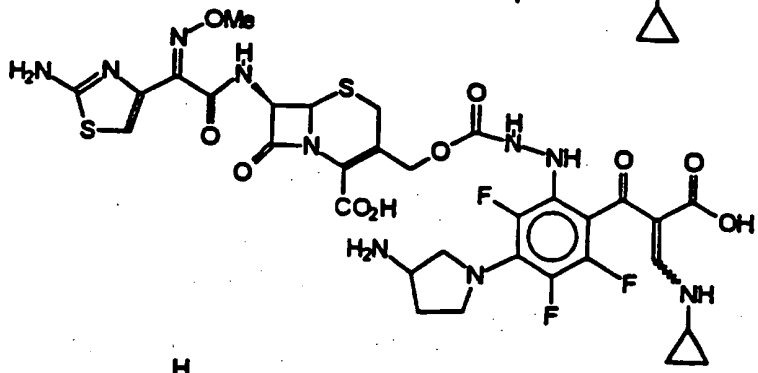


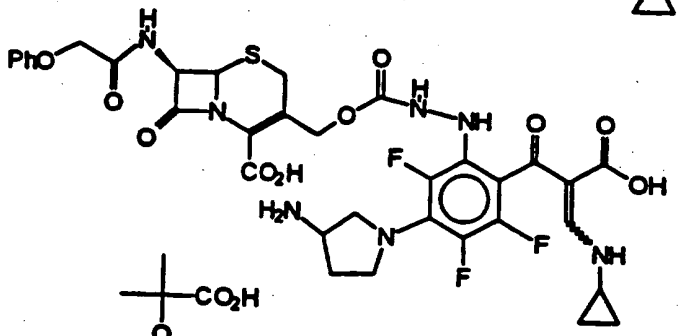


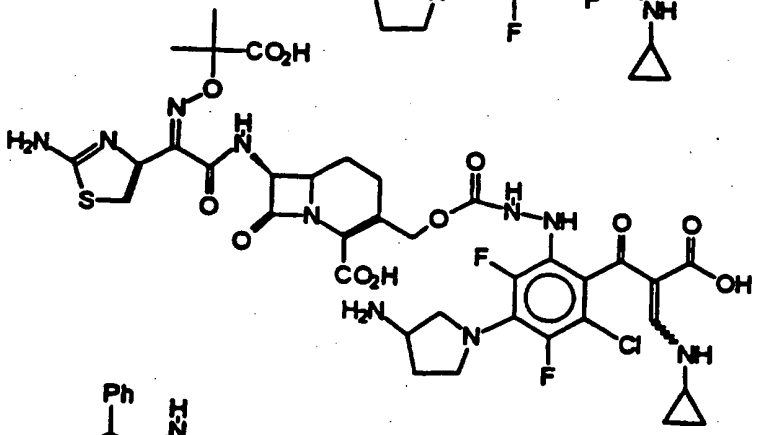


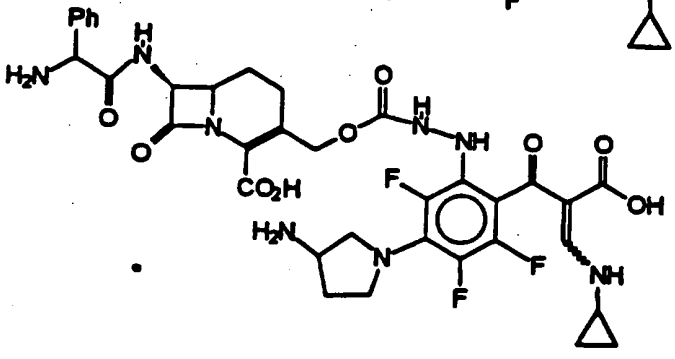


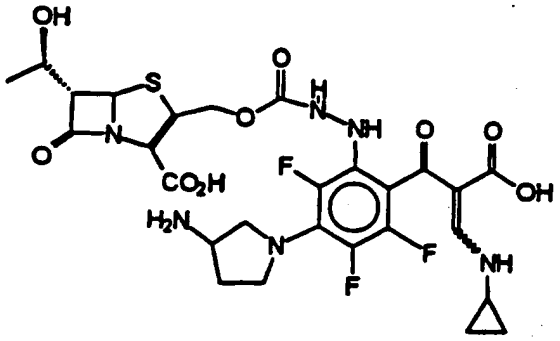


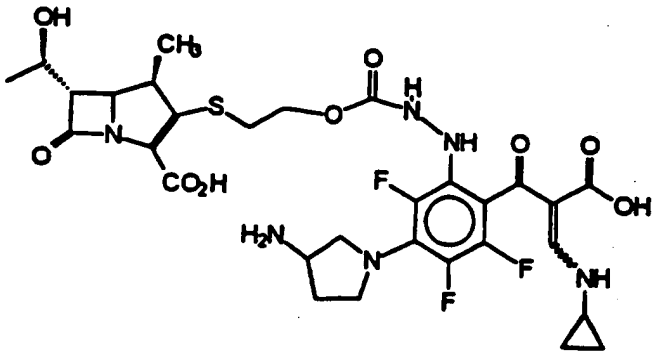


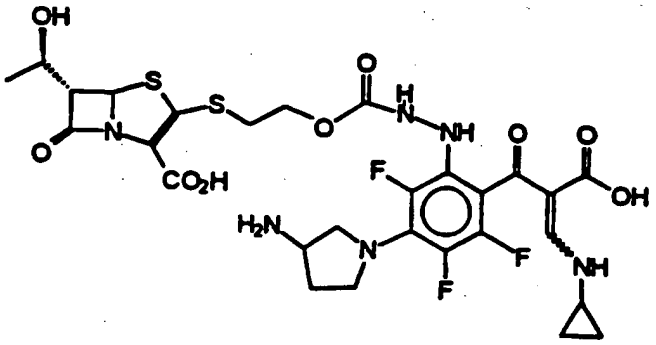


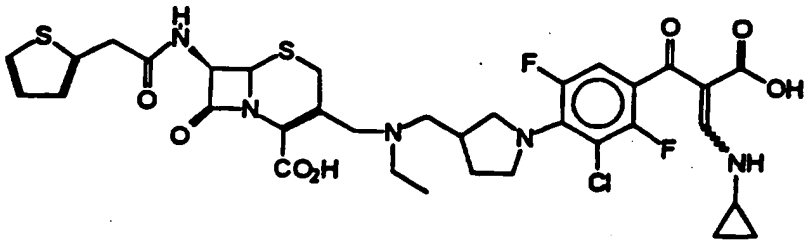


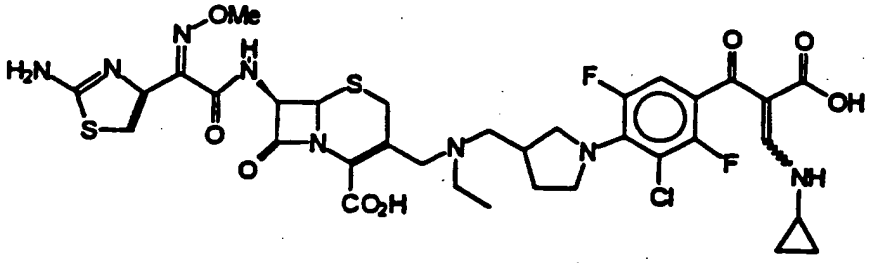


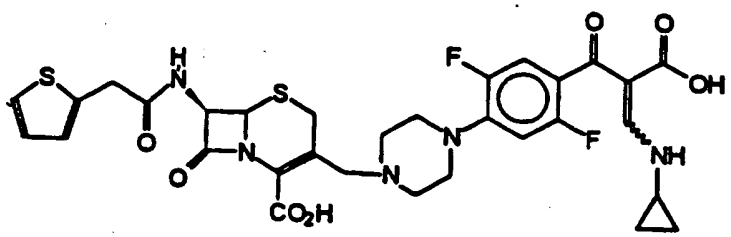


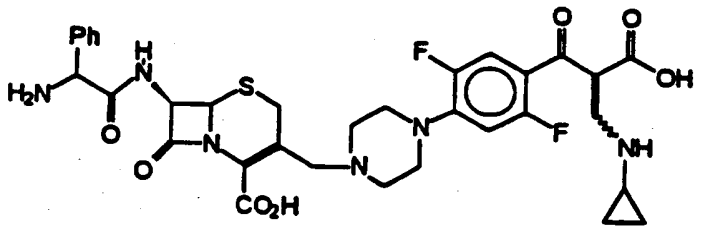


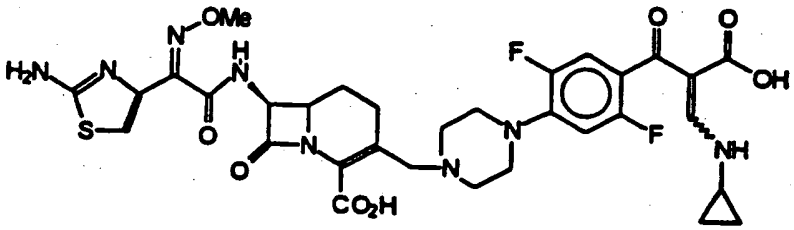


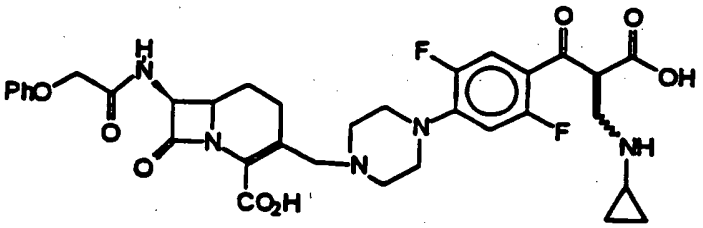


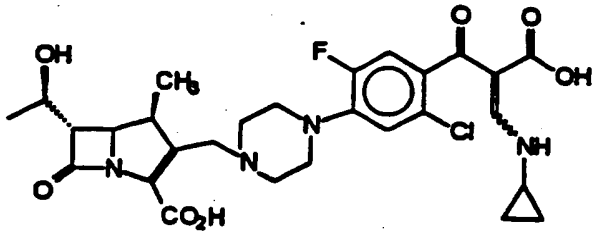


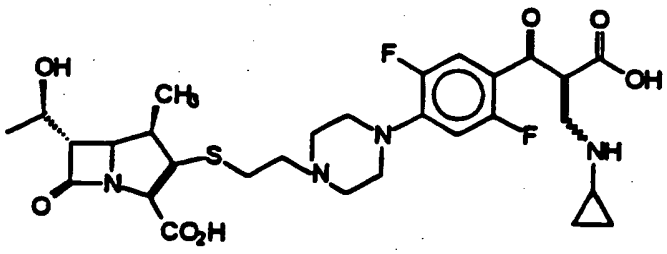


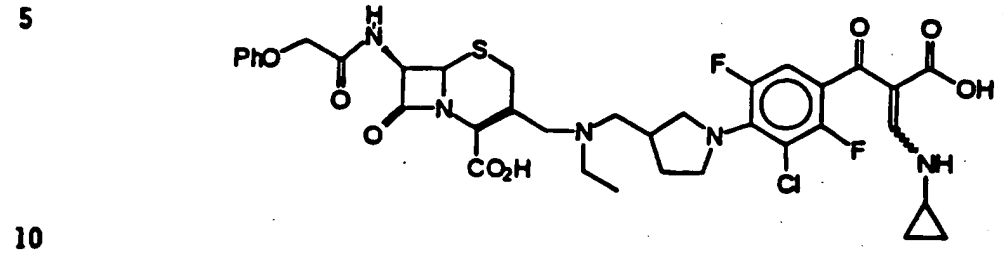


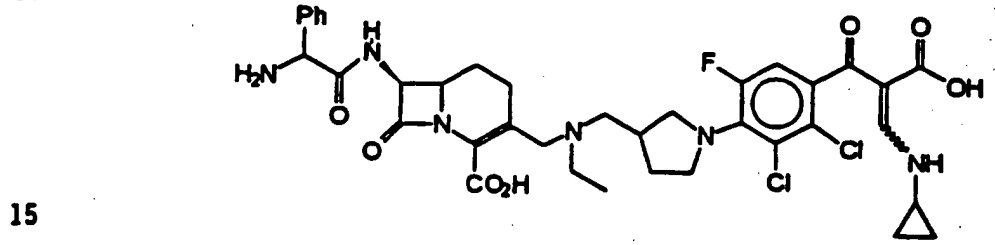


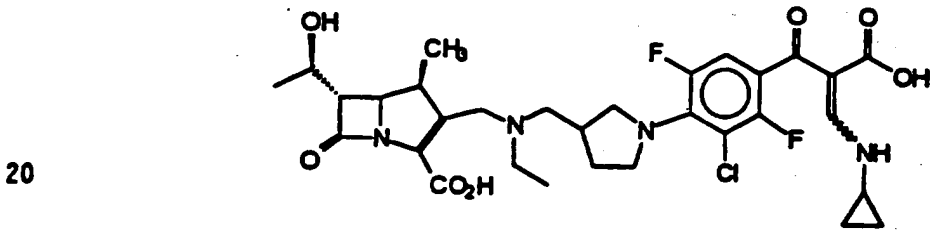


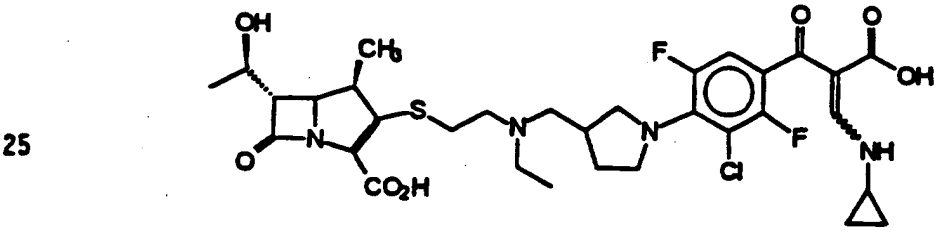


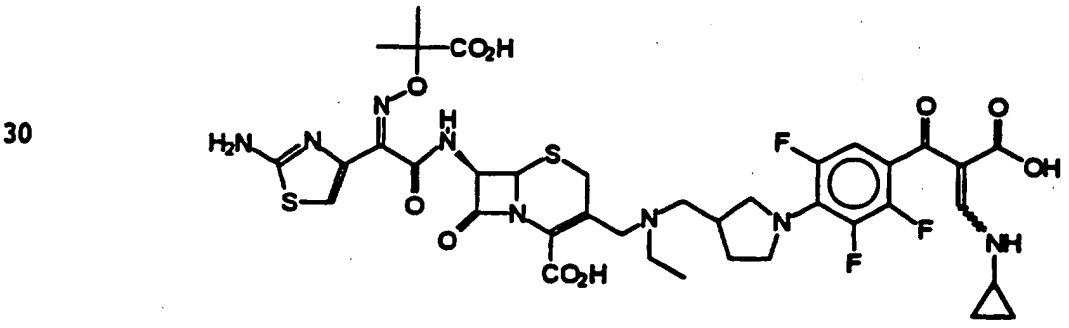


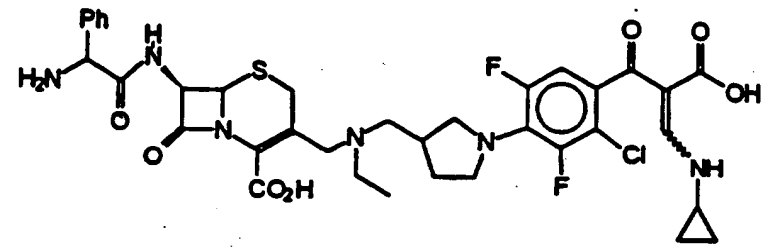


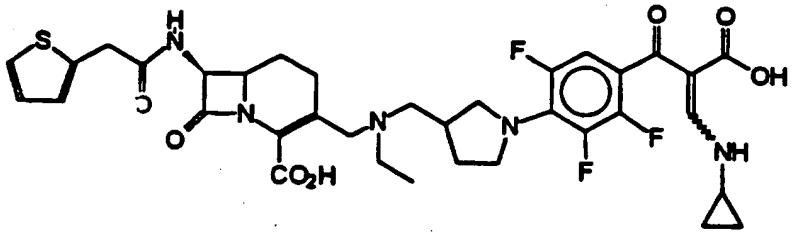


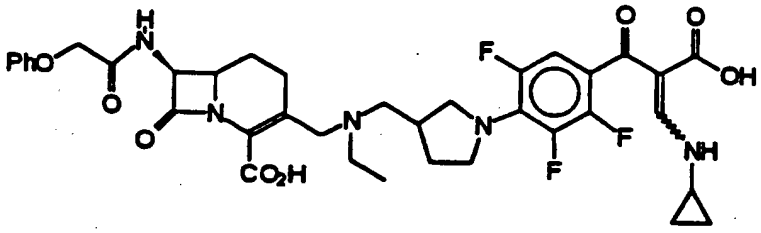


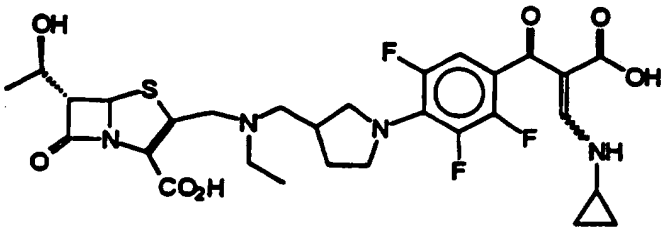


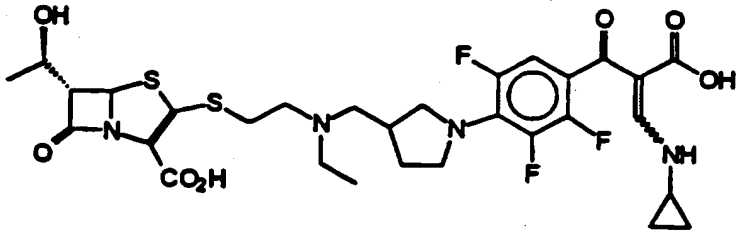


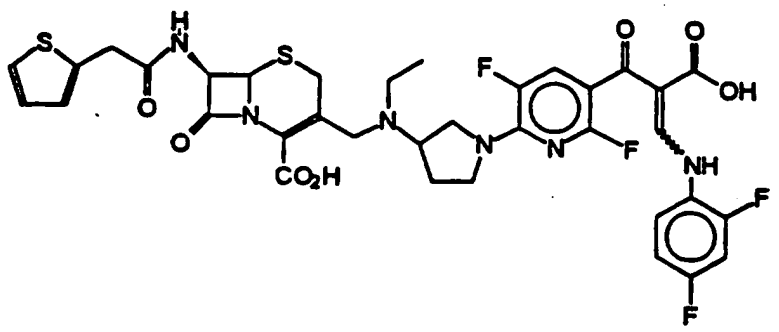


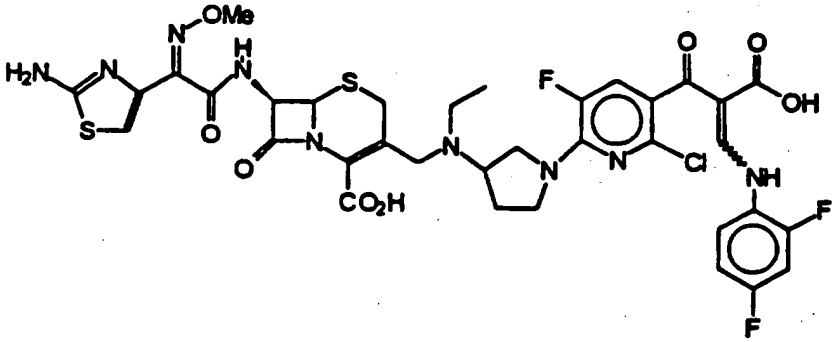


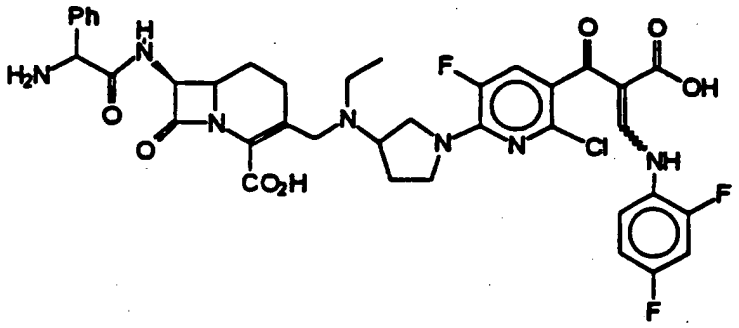


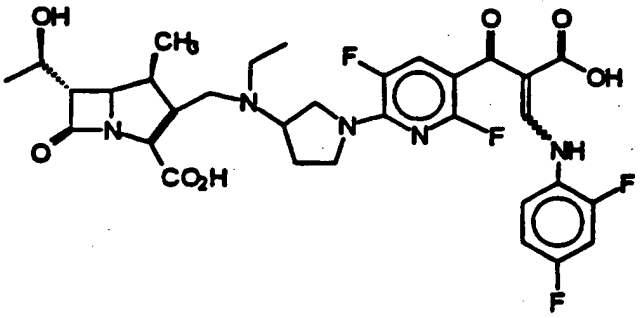


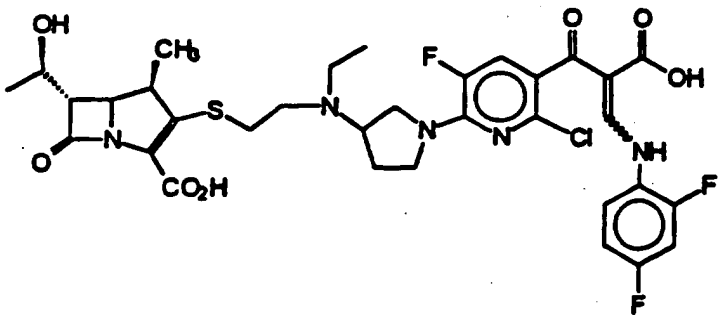


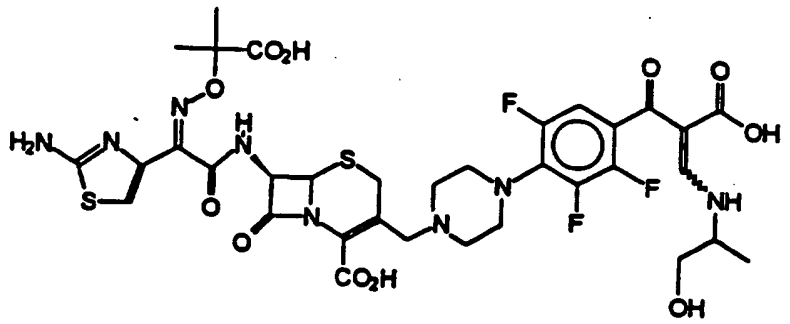


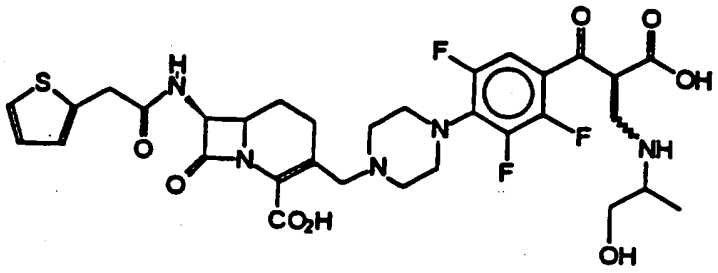


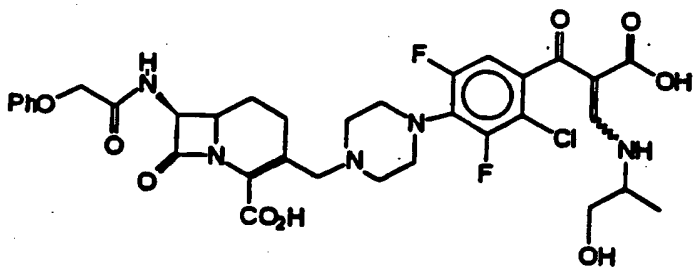


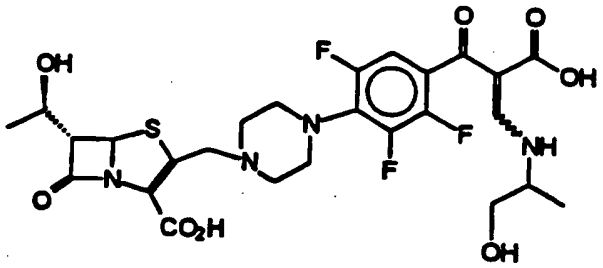


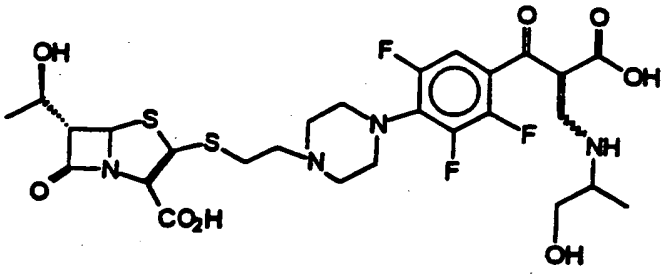


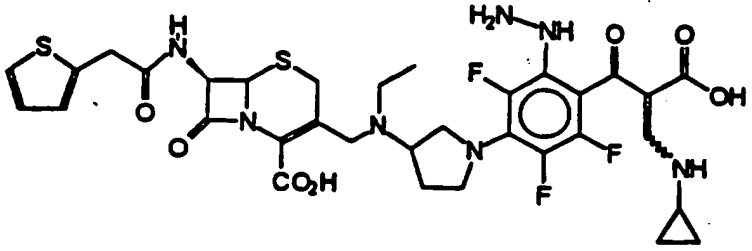


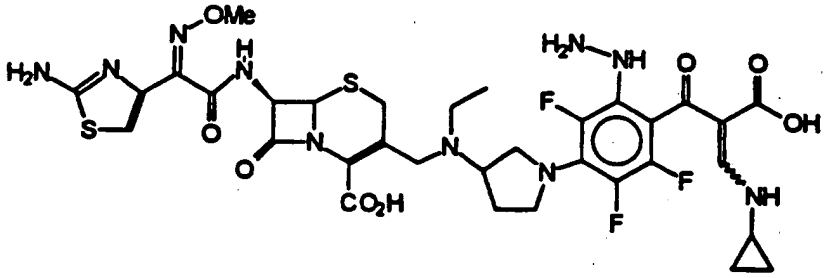


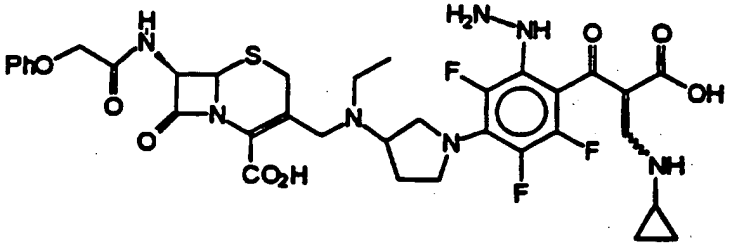


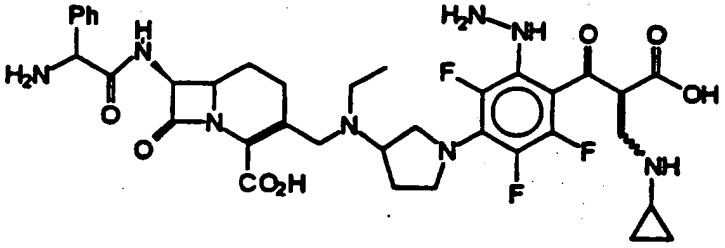


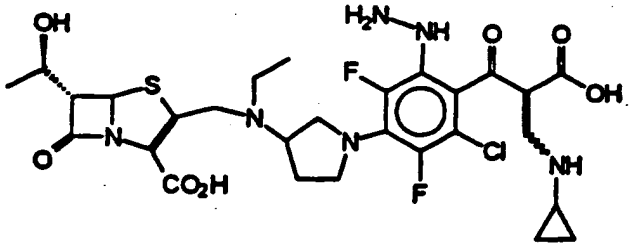


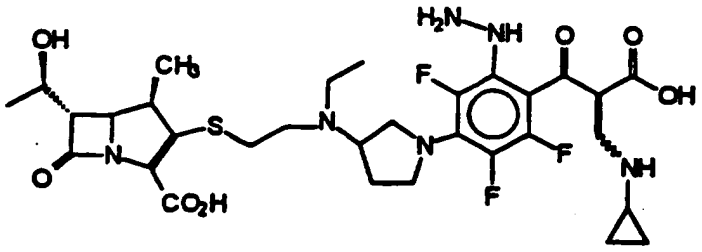


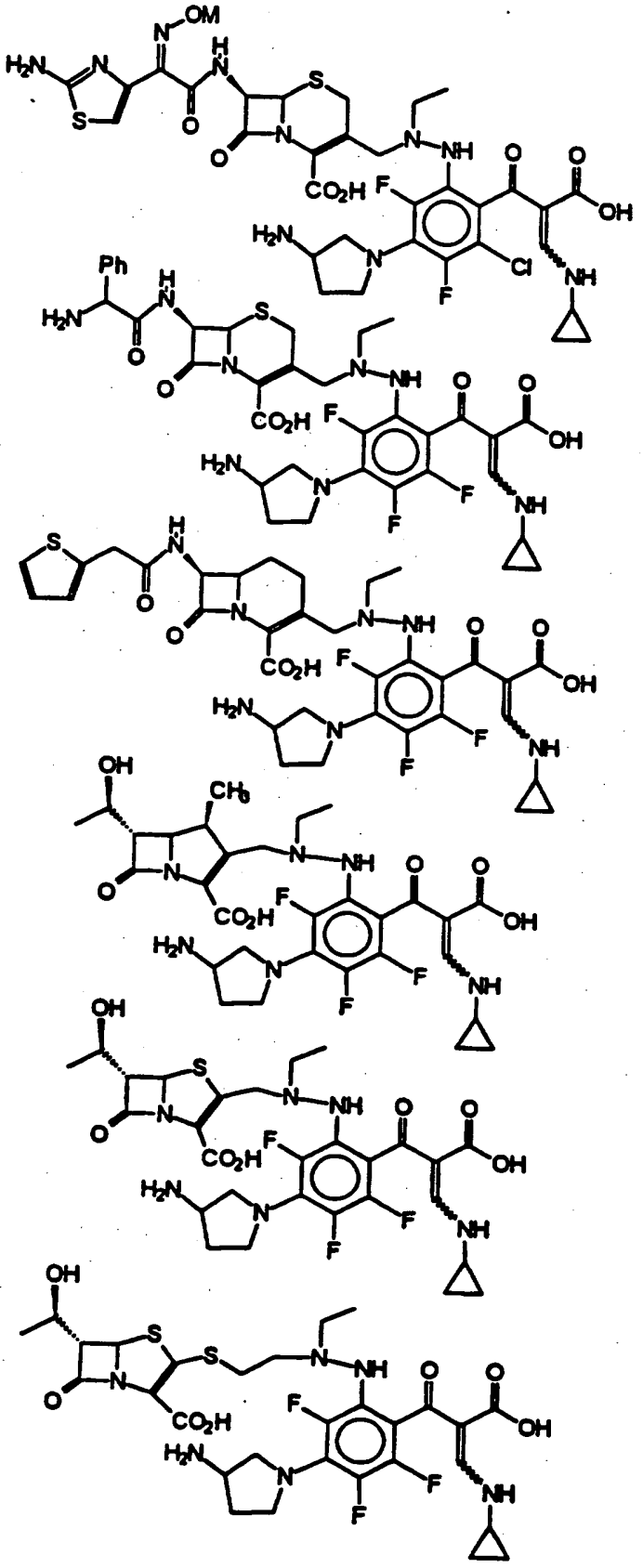


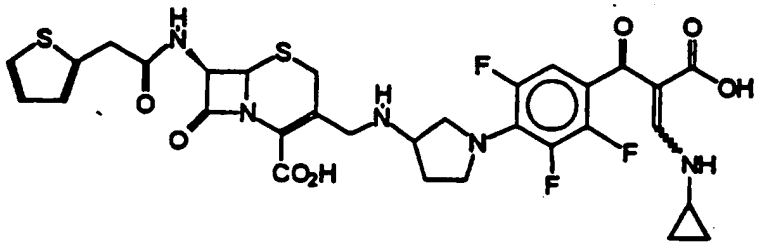


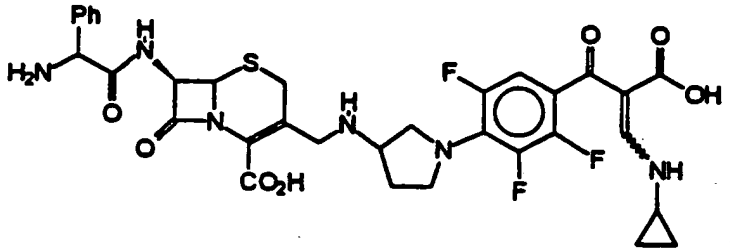


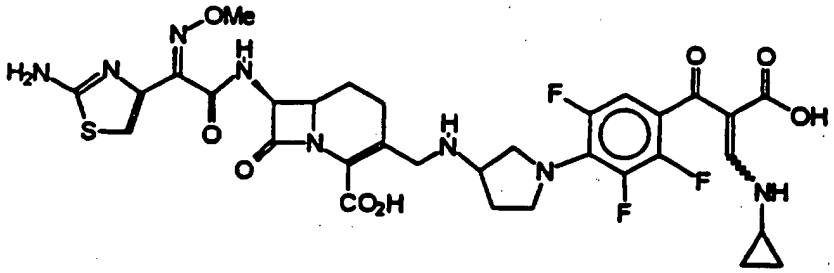


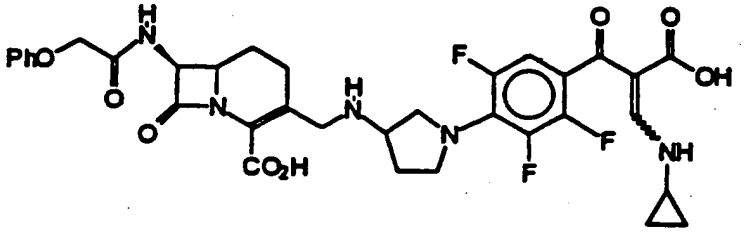


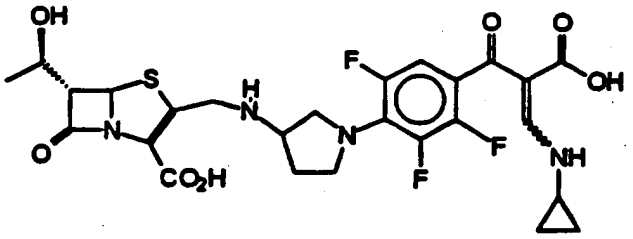


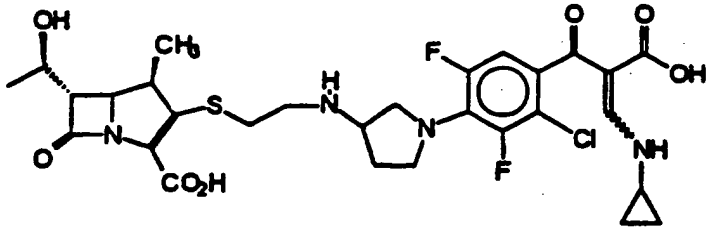


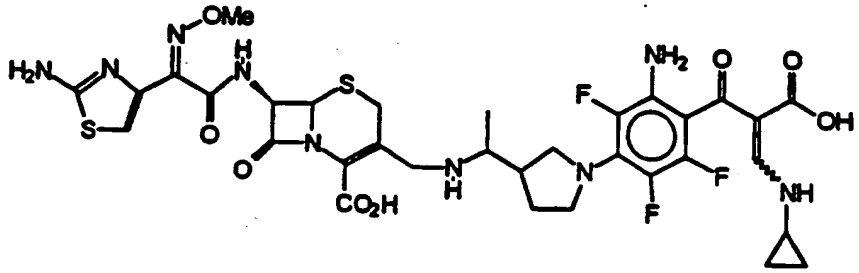


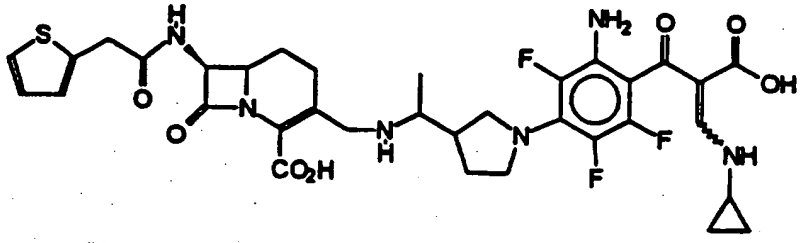


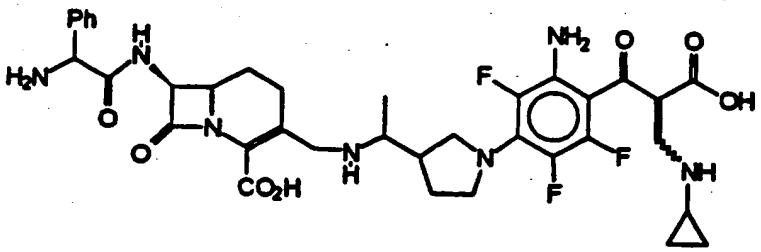


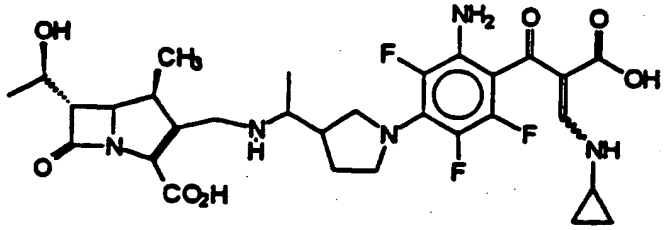


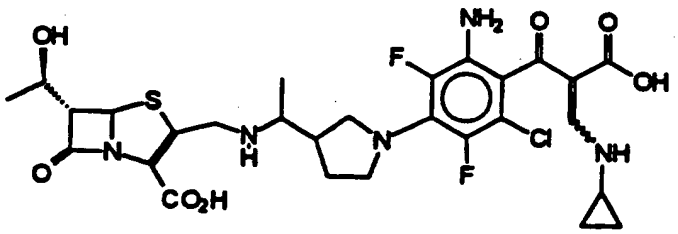


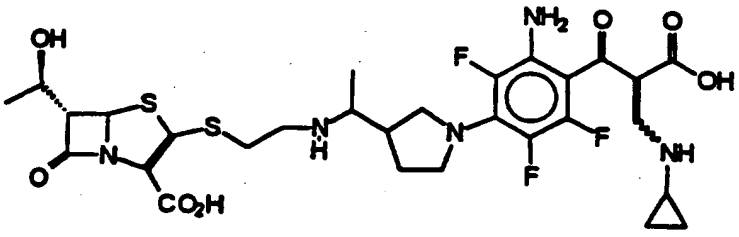


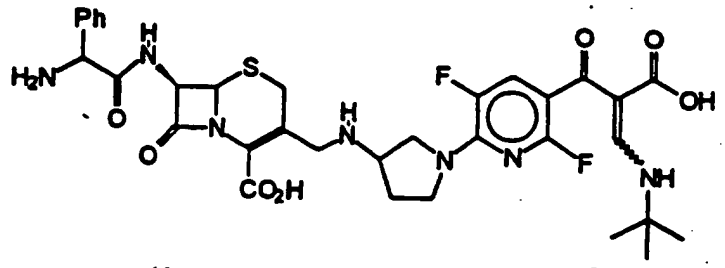


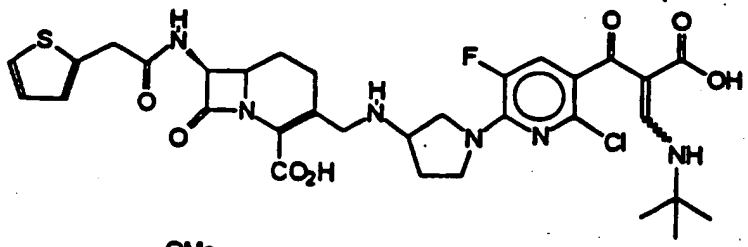


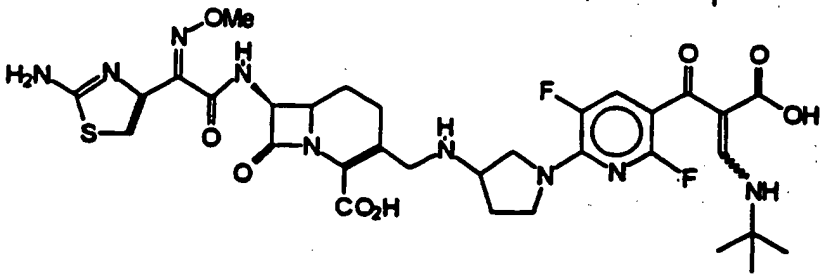


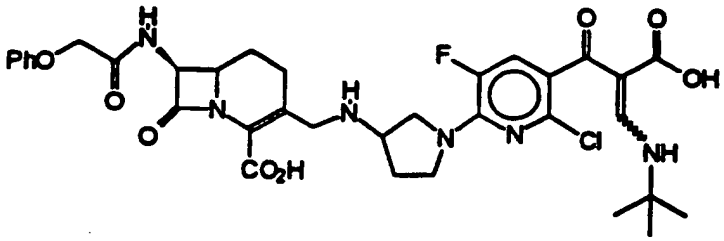


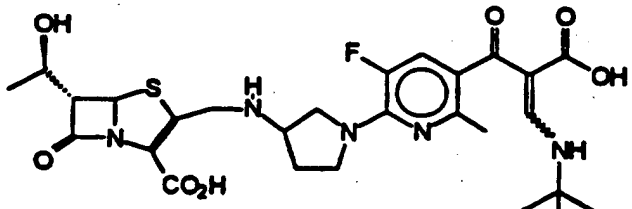


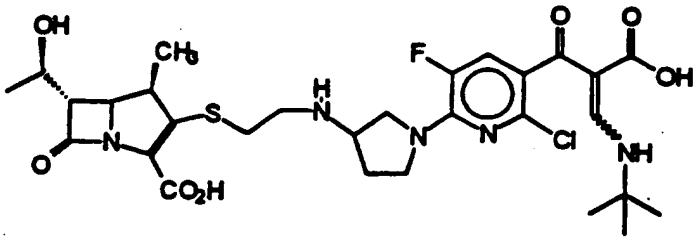


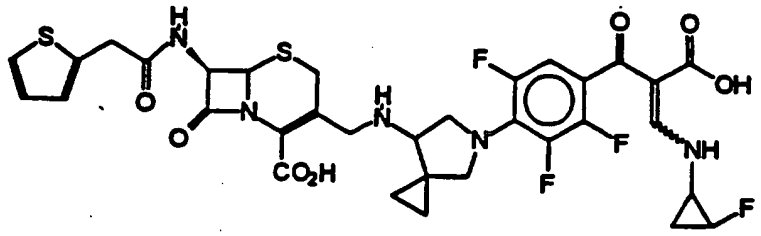


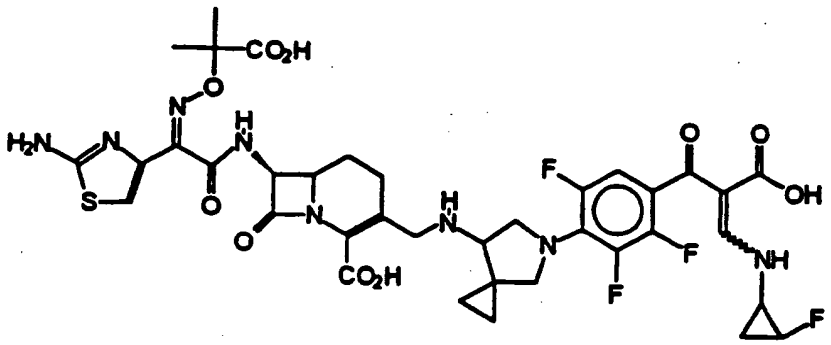


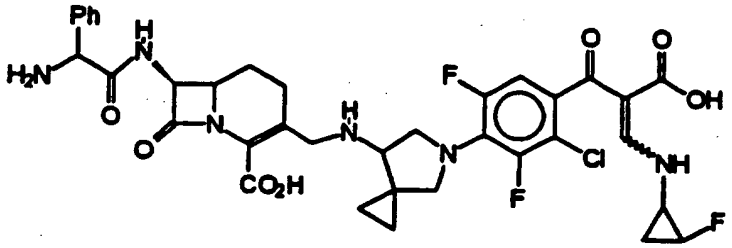


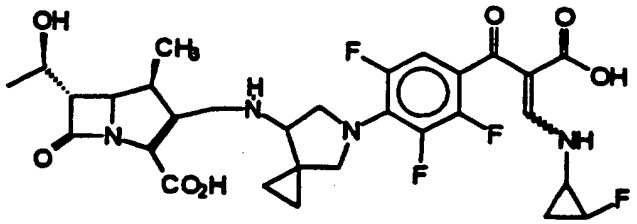


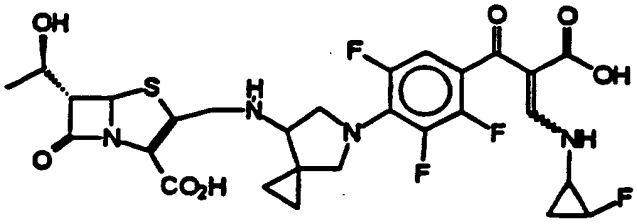


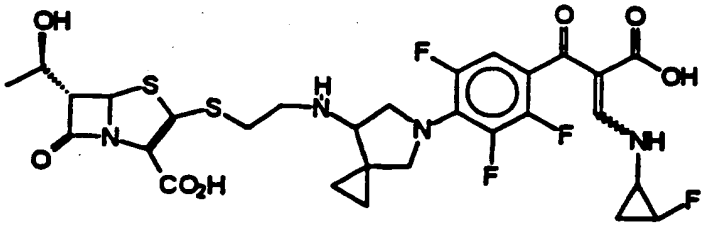


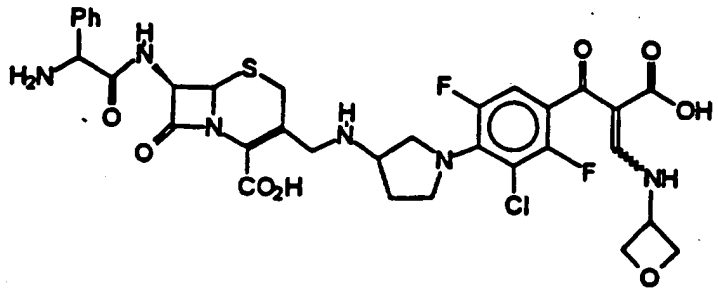


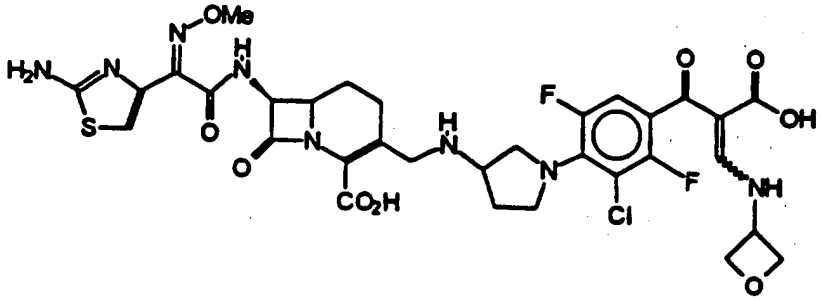


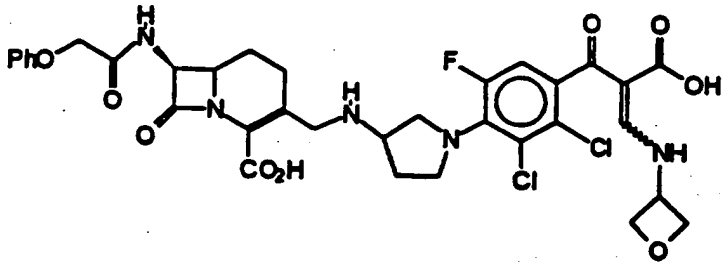


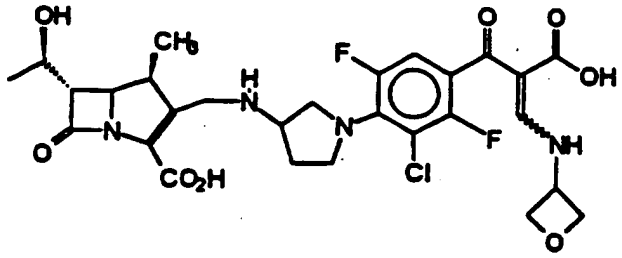


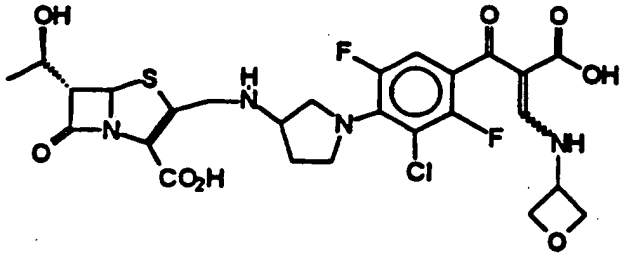


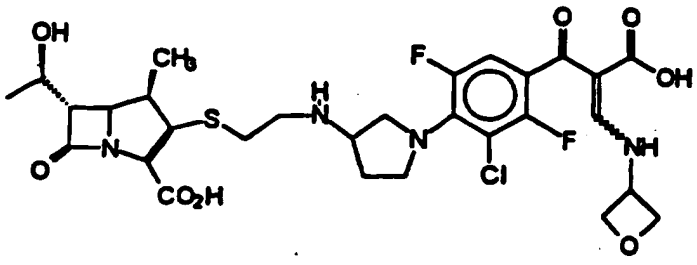


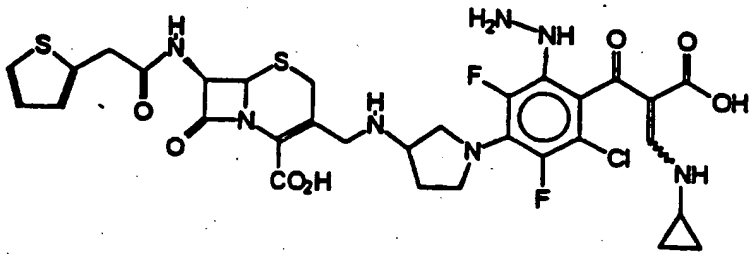


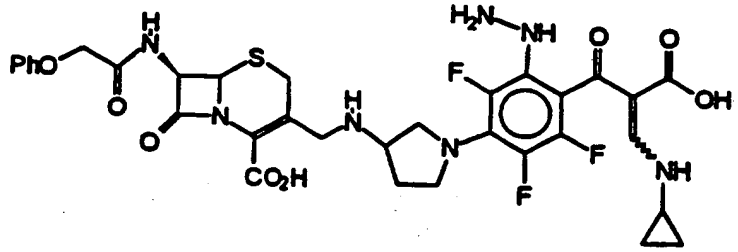


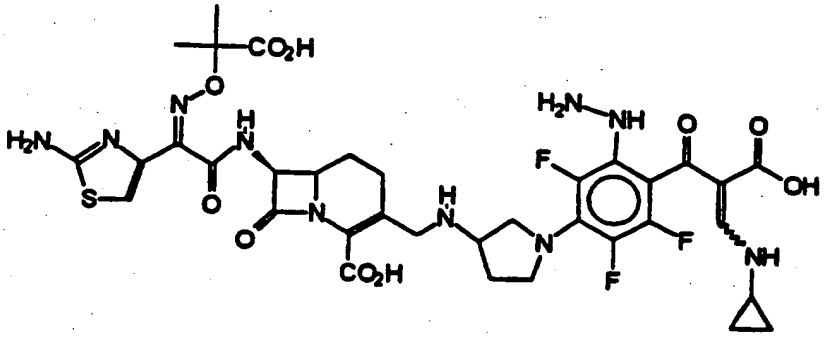


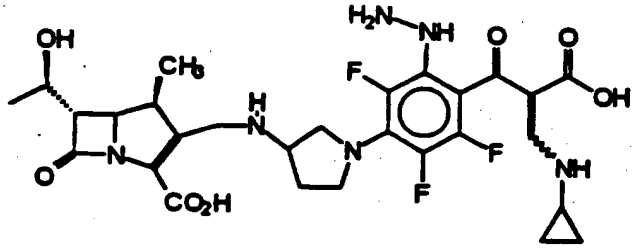


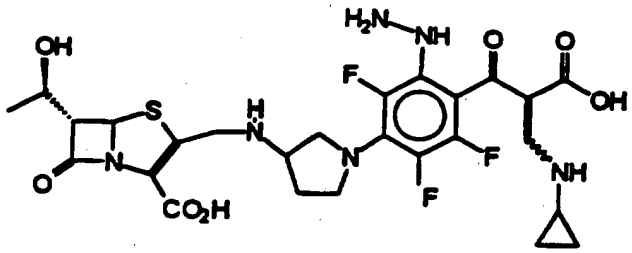


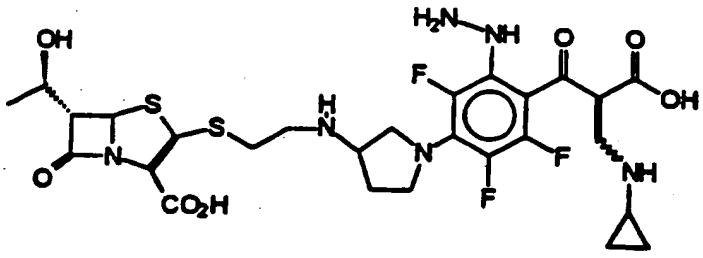


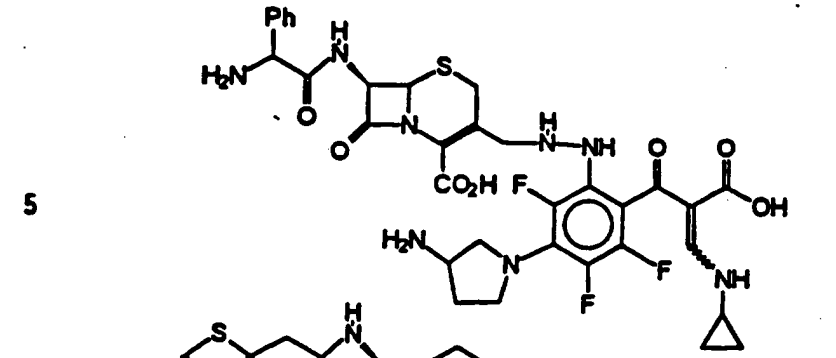


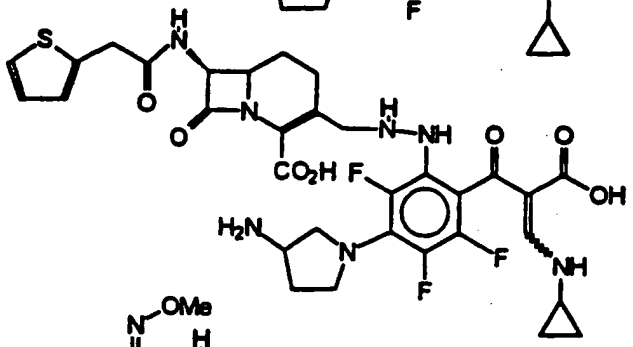


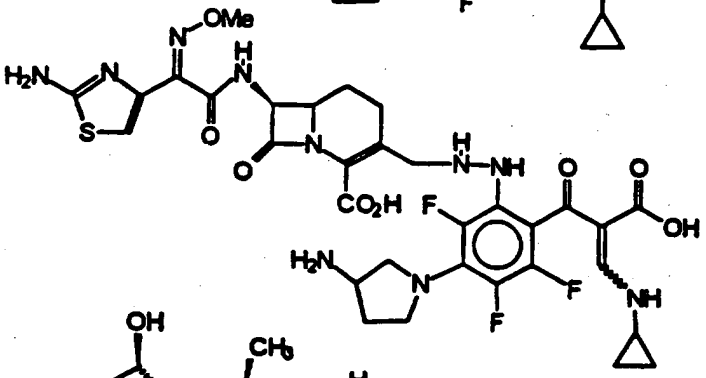


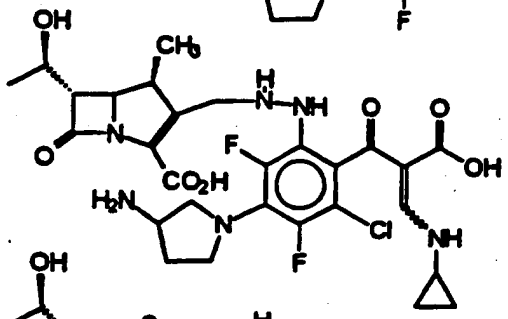


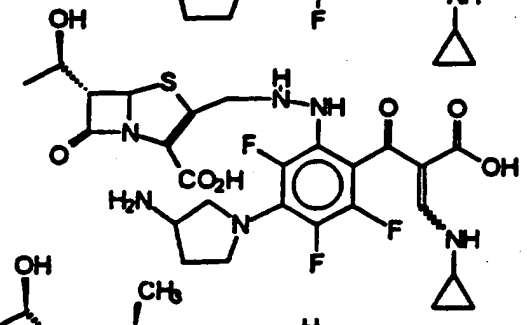


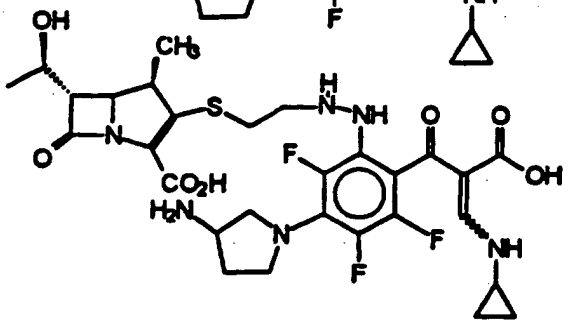












All publications mentioned hereinabove are hereby inc rporated in their entirety by reference.

It is understood that the examples and embodiments described herein are for illustrative purposes only and that various modifications or changes in light thereof will be suggested to one skilled in the art and are to be included in the spirit and purview of this application and scope of the appended claims.

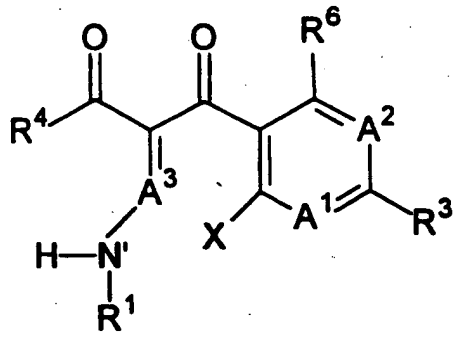
WHAT IS CLAIMED IS:

1. A process for making a compound of the formula

$$(Q - L^1) - L - (L^2 - B)$$

the method comprising the steps of:

(1) coupling a compound having a structure according to Formula (III)



(III)

characterized in that

(A) (1) A^1 is N or $C(R^7)$; where

(a) R^7 is hydrogen, hydroxy, alkoxy, nitro, cyano, halogen, alkyl, or $-N(R^8)(R^9)$, and

(b) R^8 and R^9 are, independently, hydrogen, alkyl, alkenyl, a carbocyclic ring, or a heterocyclic ring; or R^8 and R^9 together comprise a heterocyclic ring including the nitrogen to which they are bonded;

(2) A^2 is N or $C(R^2)$; where R^2 is hydrogen or halogen;

(3) A^3 is N or $C(R^5)$; where R^5 is hydrogen;

(4) R^1 is hydrogen, alkyl, a carbocyclic ring, a heterocyclic ring, alkoxy, hydroxy, alkenyl, arylalkyl, or $-N(R^8)(R^9)$;

(5) R^3 is hydrogen, halogen, alkyl, a carbocyclic ring, or a heterocyclic ring;

(6) R^4 is hydroxy;

(7) R^6 is hydrogen, halogen, nitro or $-N(R^8)(R^9)$; and

(8) X is a leaving group

(B) and

(1) when A^2 is $C(R^2)$, R^2 and R^3 may together comprise $-O-(CH_2)_n-O-$, where n is from 1 t 4;

(2) when A^3 is $C(R^5)$, R^4 and R^5 may together comprise a heterocyclic ring; and

(3) when A^1 is $C(R^7)$, R^7 and R^3 may together comprise a heterocyclic ring including A^1 and the carbon atom to which R^3 is bonded;

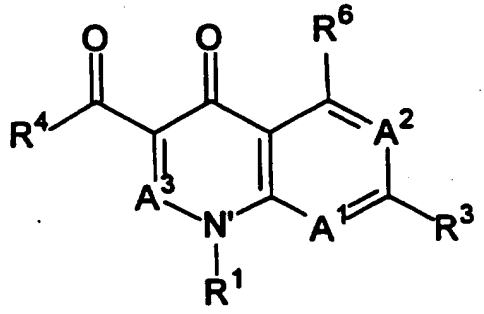
or a protected form, salt, ester, or solvate thereof;

with a lactam-containing compound having a structure according to Formula (II), to form an intermediate compound; and

(2) cyclizing the intermediate compound by reaction with an organosilicon compound to give a compound of the formula $(Q - L^1) - L - (L^2 - B)$;

characterized in that

(I) Q has a structure according to Formula (I)



(I)

wherein

(A) (1) A^1 is N or $C(R^7)$; where

(a) R^7 is hydrogen, hydroxy, alkoxy, nitro, cyano, halogen, alkyl, or $-N(R^8)(R^9)$, and

(b) R^8 and R^9 are, independently, R^{8a} where R^{8a} is hydrogen, alkyl, alkenyl, a carbocyclic ring, or a heterocyclic ring; or R^8 and R^9 together comprise a heterocyclic ring including the nitrogen to which they are bonded;

(2) A^2 is N or $C(R^2)$; where R^2 is hydrogen or halogen;

(3) A^3 is N or $C(R^5)$; where R^5 is hydrogen;

(4) R^1 is hydrogen, alkyl, a carbocyclic ring, a heterocyclic ring, alkoxy, hydroxy, alkenyl, arylalkyl, or $-N(R^8)(R^9)$;

(5) R^3 is hydrogen, halogen, alkyl, a carbocyclic ring, or a heterocyclic ring;

(6) R^4 is hydroxy; and

(7) R^6 is hydrogen, halogen, nitro or $-N(R^8)(R^9)$;

(B) and

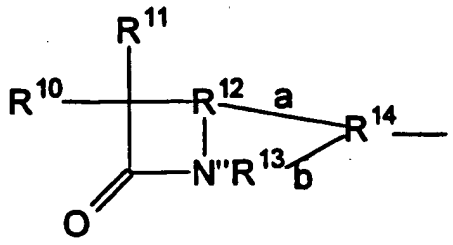
(1) when A^2 is $C(R^2)$, R^2 and R^3 may together comprise $-O-(CH_2)_n-O-$, where n is from 1 to 4;

(2) when A^3 is $C(R^5)$, R^4 and R^5 may together comprise a heterocyclic ring; and

(3) when A^1 is $C(R^7)$, R^7 and R^3 may together comprise a heterocyclic ring including A^1 and the carbon atom to which R^3 is bonded;

(C) and provided that one of R^1, R^3, or R^6 is a covalent bond to L^1;

(II) B has a structure according to Formula (II):



(II)

characterized in that

(A) R^{10} is hydrogen, halogen, alkyl, alkenyl, heteroalkyl, a carbocyclic ring, a heterocyclic ring, R^8-O-, R^8CH=N-, $(R^8)(R^9)$N-, R^{17}-C(=CHR^{20})-C(=O)NH-, R^{17}-C(=NO-R^{19})-C(=O)NH-, or $R^{18}-(CH_2)_m$-C(=O)NH-; where

(1) m is an integer from 0 to 9;

(2) R^{17} is hydrogen, alkyl, alkenyl, heteroalkyl, heteroalkenyl, a carbocyclic ring, or a heterocyclic ring;

(3) R^{18} is R^{17}, $-Y^1$, or $-CH(Y^2)(R^{17})$;

(4) R^{19} is R^{17}, arylalkyl, heteroarylalkyl,-$C(R^{22})(R^{23})$-COOH, -C(=O)O-R^{17}, or -C(=O)NH-R^{17}, where R^{22} and R^{23} are, independently, R^{17} or together comprise a carbocyclic ring or a heterocyclic ring including the carbon atom to which R^{22} and R^{23} are bonded;

(5) R^{20} is R^{19}, halogen, -Y^1, or -$CH(Y^2)(R^{17})$;

(6) Y^1 is -C(=O)OR^{21}, -C(=O)R^{21}, -N(R^{24})R^{21}, -$S(O)_p$ R^{29}, or -OR^{29}; and Y^2 is Y^1 or -OH, -SH, or -SO_3H;

(a) p is an integer from 0 to 2;

(b) R^{24} is hydrogen; alkyl; alkenyl; heteroalkyl; heteroalkenyl; a carbocyclic ring; a heterocyclic ring; -SO_3H; -C(=O)R^{25}; r, when R^{18} is -CH(N(R^{24})R^{21})(R^{17}), R^{24} may comprise a moiety bonded to R^{21} to form a heterocyclic ring; and

(c) R^{25} is R^{17}, NH(R^{17}), N(R^{17})(R^{26}), O(R^{26}), or S(R^{26}); where R^{26} is alkyl, alkenyl, a carbocyclic ring, a heterocyclic ring, or when R^{25} is -N(R^{17})(R^{26}), R^{26} may be a moiety bonded to R^{17} to form a heterocyclic ring; and

(7) R^{21} is R^{29} or hydrogen; where R^{29} is alkyl; alkenyl; arylalkyl; heteroalkyl; heteroalkenyl; heteroarylalkyl; a carbocyclic ring; a heterocyclic ring; or, when Y is -N(R^{24})R^{21} and R^{21} is R^{29}, R^{21} and R^{24} may together comprise a heterocyclic ring including the nitrogen atom to which R^{24} is bonded;

(B) R^{11} is hydrogen, halogen, alkoxy, or R^{27}C(=O)NH-, where R^{27} is hydrogen or alkyl;

(C) bond "a" is a single bond or is nil; and bond "b" is a single bond, a double bond, or is nil; except bond "a" and bond "b" are not both nil;

(D) R^{12} is -$C(R^8)$-, or -CH_2-R^{28}-; where R^{28} is -$C(R^8)$, -O-, or -N-, and R^{28} is directly bonded t N" in Formula (II) to form a 5-membered ring;

except, if bond "a" is nil, then R^{12} is

(1) $-C(R^8)(X^1)-$, where

(a) X^1 is $-R^{21}$; $-OR^{30}$; $-S(O)_rR^{30}$, where r is an integer from 0 to 2; $-OC(=O)R^{30}$; or $-N(R^{30})R^{31}$; and

(b) R^{30} and R^{31} are, independently, alkyl, alkenyl, a carbocyclic ring or a heterocyclic ring; or R^{30} and R^{31} together comprise a heterocyclic ring including the nitrogen atom to which R^{30} and R^{31} are bonded; or

(2) $-CH_2-R^{32}-$; where R^{32} is $-C(R^8)(R^{21})$, -O-, or $-NR^8$, and R^{32} is directly bonded to N" in Formula (II) to form a 5-membered ring;

(E) (1) if bond "b" is a single bond, R^{13} is $-CH(R^{33})$; or, $-C(O)NHSO_2-$, if bond "a" is nil; or $-C^*(R^{33})-$ if R^{14} contains a R^{36} moiety; where R^{33} is hydrogen or $COOR^{46}$ where R^{46} is hydrogen, alkyl or alkenyl, and C* is linked to R^{36} to form a 3-membered ring;

(2) if bond "b" is a double bond, R^{13} is $-C(R^{33})=$; or

(3) if bond "b" is nil, R^{13} is hydrogen, $-SO_3H$, $-PO(OR^{34})OH$, $-C(O)NHSO_2N(R^{34})(R^{35})$, $-OSO_3H$, $-CH(R^{35})COOH$, or $-OCH(R^{34})-COOH$; where R^{34} is hydrogen, alkyl, alkenyl, a carbocyclic ring, or a heterocyclic ring; and R^{35} is hydrogen, alkyl, alkenyl, or $-NHR^8$; or, if R^{13} is $-C(O)NH-SO_2N-(R^{34})(R^{35})$, R^{34} and R^{35} may together comprise a heterocyclic ring including the nitrogen to which R^{34} and R^{35} are bonded; and

(F) (1) if bond "a" or bond "b" is nil, then R^{14} is a covalent bond;

(2) if bond "a" and "b" are single bonds, R^{14} is $-W-C'''=C(R^{8a})-R^{37}-$, or $-W-C'''(R^{36})-R^{37}-$; or

(3) if bond "a" is a single bond and bond "b" is a double bond, R^{14} is $-C(R^8)(R^{38})-W-C'''-R^{37}-$; $-W-C(R^8)-(R^{38})-C'''-R^{37}-$; or $-W-C'''-R^{37}-$;

(4) where

(a) W is O; $S(O)_s$, where s is an integer from 0 to 2; or $C(R^{38})$, where R^{38} is hydrogen, alkyl or alkoxy;

(b) R^{36} is hydrogen; alkyl; alkenyl; -COOH; or, if R^{13} is $-C^*(R^{33})$, R^{36} may be linked to C* to form a 3-membered carbocyclic ring;

(c) R^{37} is covalent bond, alkyl, alkenyl, a carbocyclic ring, or a heterocyclic ring; and

(d) C''' is directly bonded to R^{13} to form a 5- or 6-membered ring; and

(III) (A) L is $-C(=Z)-$; $-S(O)_v-$; $-N(R^{44})-$; $-N^+(R^{44})(R^{45})-$; $-N(R^{44})-N(R^{44})-$; -O-; =N-; or a covalent bond; and L is bonded to L^3 and L^4; where

(1) Z is O, S, or $^+N(H)_2$;

(2) v is 0, 1 or 2;

(3) R^{44} is hydrogen, substituted or unsubstituted lower alkyl, aryl, acyl, hydroxy, alkoxy, aryloxy, or acyloxy; and

(4) R^{45} is hydrogen, unsubstituted or substituted lower alkyl, or substituted or unsubstituted aryl;

(B) L^1 is L^3 or $R^{15}L^3$; where

(1) when L is $-C(=Z)-$, L^3 is a covalent bond, oxygen, sulfur, or nitrogen; and when L is other than $-C(=Z)-$, L^3 is a covalent bond;

(2) R^{15} is alkyl, alkenyl, heteroalkyl, a heterocyclic ring, a carbocyclic ring, or R^{15} together with L^3 is a heteroalkyl or a heterocyclic ring; and

(3) L^1 is bonded to Q at the point of attachment of R^1, R^3 or R^6, whichever is a covalent bond;

(C) L^2 is L^4, $-X^2_t-R^{39}-L^4$, or $-X^3_t-R^{39}-L^4$; where

(1) when L is $-C(=Z)-$, L^4 is a covalent bond, oxygen, sulfur, or nitrogen; and when L is other than $-C(=Z)-$, L^4 is a covalent bond;

(2) X^2 is oxygen, or $S(O)_v$, where v is 0, 1, or 2;

(3) X^3 is nitrogen; $-N(R^{40})-$; $-N^+(R^{41})(R^{42})-$; or $R^{43}-N(R^{41})$; and is linked to R^{14} by a single or double bond; or, if R^{14} is covalent bond, X^3 is linked to B by a single or double bond; where

(a) R^{40} is R^8; $-OR^8$; or $-C(=O)R^8$;

(b) R^{41} and R^{42} are, independently, hydrogen; alkyl; alkenyl; carbocyclic rings; heterocyclic rings; or, if R^6 is $R^{16}X$, then R^{41} and R^{42} together with "Q" may comprise a heterocyclic ring as R^{16};

(c) R^{43} is $N(R^{41})$, oxygen or sulfur;

(4) t is 0 or 1;

(5) R^{39} is alkyl, alkenyl, heteroalkyl, heteroalkenyl, a carbocyclic ring, or a heterocyclic ring; and

(6) (a) if bond "a" or bond "b" is nil, then L^2 is bonded directly to R^{12} or R^{13}; or

(b) if bond "a" and bond "b" are not nil, then L^2 is bonded to R^{14};

(D) provided that if L^1, L^2 and R^{37} are each a covalent bond, then L cannot be a covalent bond;

or a protected form, salt, pharmaceutically-acceptable salt, biohydrolyzable ester, or solvate thereof.

2. The process according to Claim 1, characterized in that the coupling step is carried out in a halocarbon solvent, an ether solvent, an aromatic solvent, a dialkylamide solvent, or a mixture thereof; preferably the solvent is methylene chloride, chloroform, dichloroethane, diethyl ether, tetrahydrofuran, benzene, toluene; N,N-dimethylformamide; or a mixture thereof.

3. The process according to Claim 1, characterized in that the coupling step is performed at a temperature from about -78°C to about 50°C; preferably at a temperature of from about -50°C to about 25°C.

4. The process according to Claim 1, characterized in that an organosilicon compound is reacted with a compound of Formula (III) prior to the coupling step; and the coupling step is performed at a temperature of less than about -15°C; preferably at a temperature of from about -78°C to about -15°C.

5. The process according to Claim 1, characterized in that R^{14} is $-W-C'''-R^{37}-$ or $-W-C(R^8)(R^{38})-C'''-R^{37}-$; wherein preferably W is $S(O)_s$, where s is 0; or W is $C(R^{38})$.

6. The process according to Claim 1, characterized in that A^1 is nitrogen, A^2 is $C(R^2)$, and A^3 is $C(R^5)$, or, preferably, A^1 is $C(R^7)$, A^2 is $C(R^2)$, and A^3 is $C(R^5)$.

7. The process of Claim 6, characterized in that R^1 is alkyl, aryl, cycloalkyl, or alkylamino; R^7 is hydrogen or halogen; and R^3 is a heterocyclic ring, preferably a substituted or unsubstituted pyrrolidine or a substituted or unsubstituted piperazine.

8. The process according to Claim 1, characterized in that R^3 is a covalent bond to L^1 or R^6 is a covalent bond to L^1.

9. The process according to Claim 1, characterized in that

(a) L is -C(=Z)-, where Z is O; and wherein L^3 is nitrogen; r

(b) L is $-N(R^{44})-$, where R^{44} is hydrogen or unsubstituted or substituted lower alkyl.

10. The process according to Claim 1, characterized in that

(a) the quinolone moiety is:

1-Cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-piperazinyl-quinoline-3-carboxylic acid;

1-Cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-piperazinyl-quinoline-3-carboxylic acid allyl ester;

1-Cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-piperazinyl-quinoline-3-carboxylic acid diphenylmethyl ester;

1-Cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-piperazinyl-quinoline-3-carboxylic acid t-butyl ester;

1-Cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-piperazinyl-quinoline-3-carboxylic acid 2,2,2-trichloroethyl ester;

7-(3-Amino-1-pyrrolidinyl)-1-cyclopropyl-6,8-difluoro-1,4-dihydro-4-oxo-quinoline-3-carboxylic acid;

7-(3-Amino-1-pyrrolidinyl)-1-cyclopropyl-6,8-difluoro-1,4-dihydro-4-oxo-quinoline-3-carboxylic acid allyl ester;

7-(3-Amino-1-pyrrolidinyl)-1-cyclopropyl-6,8-difluoro-1,4-dihydro-4-oxo-quinoline-3-carboxylic acid allyl ester;

5-Amino-7-(3-amino-1-pyrrolidinyl)-1-cyclopropyl-6,8-difluoro-1,4-dihydro-4-oxo-quinoline-3-carboxylic acid allyl ester;

5-Amino-1-cyclopropyl-6,8-difluoro-1,4-dihydro-7-(2,6-dimethyl-4-piperazinyl)-4-oxo-quinoline-3-carboxylic acid;

7-(3-Amino-1-pyrrolidinyl)-1-(2,4-difluorophenyl)-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid allyl ester; or

7-[3-(t-Butyloxycarbonyl)amino-1-pyrrolidinyl]-1-cyclopropyl-6,8-difluoro-1,4-dihydro-5-hydrazino-4-oxo-quinoline-3-carboxylic acid allyl ester; and

(b) the lactam moiety is:

[5R-[5a,6a]]-6-[(R)-1-(t-butyldimethylsilyloxy)ethyl]-3-hydroxymethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid allyl ester;

[5R-[5a,6a]]-6-[(R)-1-[(allyloxycarbonyl)oxy]ethyl]-3-hydroxymethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid allyl ester;

[5R-[5a,6a]]-6-[(R)-1-[(2,2,2-trichloroethyloxycarbonyl)oxy]ethyl]-3-hydroxymethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid 2, 2,2-trichloroethyl ester;

[5R-[5a,6a]]-6-[(R)-1-(t-butyldimethylsilyloxy)ethyl]-3-hydroxymethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid diphenylmethyl ester;

[5R-[5a,6a]]-6-[(R)-1-(t-butyldimethylsilyloxy)ethyl]-3-hydroxymethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid t-butyl ester;

[5R-[4b,5a,6a]]-6-[(R)-1-(t-butyldimethylsilyloxy)ethyl]-3-hydroxymethyl-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid allyl ester;

[5R-[5a,6a]]-6-[(R)-1-(t-butyldimethylsilyloxy)ethyl]-3-(2-hydroxyethylthio)-7-oxo-4-thia-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid allyl ester; or

[5R-[4b,5a,6a]]-6-[(R)-1-(t-butyldimethylsilyloxy)ethyl]-3-(2-hydroxy-ethylthio)-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid allyl ester.

11. A process, according to Claim 1, characterized in that said compound is:

[5R-[5a,6a]]-3-[[[4-(3-Carboxy-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-quinolinyl)-1-piperazinyl]carbonyloxy]methyl]-6-[(R)-1-hydroxyethyl]-7-oxo-4-thia-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic Acid, Disodium Salt;

[5R-[4b,5a,6a]]-3-[[[4-(3-Carboxy-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-quinolinyl)-1-piperazinyl]carbonyloxy]methyl]-6-[(R)-1-hydroxyethyl]-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic Acid, Disodium Salt;

[5R-[5a,6a]]-3-[[[[4-(3-Carboxy-1-cyclopropyl-6,8-difluoro-1,4-dihydro-4-oxo-7-quinolinyl)-(S)-3-pyrrolidinyl]amino]-carbonyloxy]methyl]-6-[(R)-1-hydroxyethyl]-7-oxo-4-thia-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic Acid, Disodium Salt;

[5R-[4b,5a,6a]]-3-[[[[4-(3-Carboxy-1-cyclopropyl-6,8-difluoro-1,4-dihydro-4-oxo-7-quinolinyl)-(S)-3-pyrrolidinyl]amino]-carbonyloxy]methyl]-6-[(R)-1-hydroxyethyl]-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic Acid, Disodium Salt;

[5R-[5a,6a]]-3-[[[[4-[3-Carboxy-1-(2,4-difluorophenyl)-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridin-1-yl]-(S)-3-pyrrolidinyl]amino]-carbonyloxy]methyl]-6-[(R)-1-hydroxyethyl]-7-oxo-4-thia-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic Acid, Disodium Salt;

[5R-[4b,5a,6a]]-3-[[[[4-[3-Carboxy-1-(2,4-difluorophenyl)-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridin-1-yl]-(S)-3-pyrrolidinyl]amino]-carbonyloxy]methyl]-6-[(R)-1-hydroxyethyl]-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic Acid, Disodium Salt;

[5R-[5a,6a]]-3-[[[4-(5-Amino-3-carboxy-1-cyclopropyl-6,8-difluoro-1,4-dihydro-4-oxo7-quinolinyl)-2,6-dimethyl-4-piperazinyl]carbonyloxy]methyl]-6-[(R)-1-hydroxyethyl]-7-oxo-4-thia-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic Acid, Disodium Salt;

[5R-[4b,5a,6a]]-3-[[[4-(5-Amino-3-carboxy-1-cyclopropyl-6,8-difluoro-1,4-dihydro-4-oxo-7-quinolinyl)-2,6-dimethyl-4-piperazinyl]carbonyloxy]methyl]-6-[(R)-1-hydroxyethyl]-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic Acid, Disodium Salt;

[5R-[5a,6a]]-3-[[[2-[7-((S)-3-Amino-1-pyrrolidinyl)-3-carboxy-1-cyclopropyl-6,8-difluoro-1,4-dihydro-4-oxo-5-quinolinyl]-1-hydrazino]-carbonyloxy]methyl]-6-[(R)--hydroxyethyl]-7-oxo-4-thia-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic Acid, Disodium Salt;

[5R-[4b,5a,6a]]-3-[[[2-[7-((S)-3-Amino-1-pyrrolidinyl)-3-carboxy-1-cyclopropyl-6,8-difluoro-1,4-dihydro-4-oxo-5-quinolinyl]-1-hydrazino]-carbonyloxy]methyl]-6-[(R)-1-hydroxyethyl]-4-methyl-7-oxo-1-azabicyclo-[3.2.0]hept-2-ene-2-carboxylic Acid, Disodium Salt;

[4R-[4α,5β,6β(R*)]]-3-[[[4-(3-Carboxy-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-quinolinyl)-1-piperazinyl]carbonyloxy]methyl]-6-(1-

hydroxyethyl)-7-oxo-4-thia-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic Acid, Disodium salt;

[6R-[6α,7β]]-3-[[[4-(3-Carboxy-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-quinolinyl)-1-piperazinyl]carbonyloxy]methyl]-8-oxo-7-[(2-thienylacetyl)amino]-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic Acid, Disodium Salt;

[6R-[6α,7β]]-3-[[[4-[3-Carboxy-1-(1,1-dimethylethyl)-6-fluoro-1,4-dihydro-4-oxo-1,8-napthyridin-7-yl]-1-piperazinyl]carbonyloxy]-methyl]-8-oxo-7-[(2-thienylacetyl)amino]-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic Acid, Disodium Salt;

[5R-[5α,6α(R*)]]-3-[[4-(3-Carboxy-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-quinolinyl)-1-piperazinyl]methyl]-6-(1-hydroxyethyl)-7-oxo-4-thia-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic Acid, Disodium Salt;

[6R-[6α,7β]]-3-[[4-(3-Carboxy-1-cyclopropyl-6,8-difluoro-1,4-dihydro-4-oxo-7-quinolinyl)-1-piperazinyl]]methyl]-8-oxo-7-[2-(phenoxyacetyl)amino]-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic Acid, Disodium Salt;

[4S-[3(R*),4α,5β,6β(S*)]]-3-[[[1-[3-Carboxy-1-(2,4-difluorophenyl)-6-fluoro-1,4-dihydro-4-oxo-1,8-napthyridin-7-yl]-3-pyrrolidinyl]amino]methyl]-6-(1-hydroxyethyl)-4-methyl-7-oxo-1-azabicyclo-[3.2.0]hept-2-ene-2-carboxylic Acid, Disodium salt; or

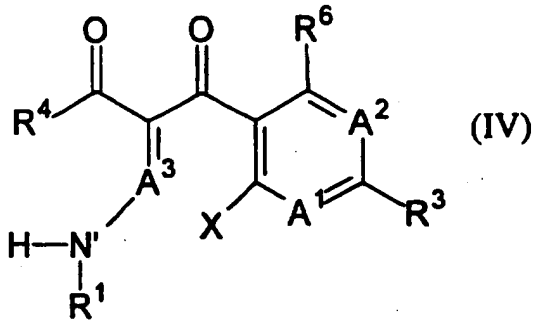
[6R-[3(S*),6α,7β]]-3-[[[1-[3-Carboxy-1-(1,1-dimethylethyl)-6-fluoro-1,4-dihydro-4-oxo-1,8-napthyridin-7-yl]-3-pyrrolidinyl]amino]methyl]-8-oxo-7-[(2-thienylacetyl)amino]-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic Acid.

12. A compound having a structure according to the formula

$$(M - L^1) - L - (L^2 - B)$$

characterized in that

(I) M has a structure according to Formula (IV)



(IV)

characterized in that

(A) (1) A^1 is N or $C(R^7)$; where

(a) R^7 is hydrogen, hydroxy, alkoxy, nitro, cyano, halogen, alkyl, or $-N(R^8)(R^9)$, and

(b) R^8 and R^9 are, independently, R^{8a} where R^{8a} is hydrogen, alkyl, alkenyl, a carbocyclic ring, or a heterocyclic ring; or R^8 and R^9 together comprise a heterocyclic ring including the nitrogen to which they are bonded;

(2) A^2 is N or $C(R^2)$; where R^2 is hydrogen or halogen;

(3) A^3 is N or $C(R^5)$; where R^5 is hydrogen;

(4) R^1 is hydrogen, alkyl, a carbocyclic ring, a heterocyclic ring, alkoxy, hydroxy, alkenyl, arylalkyl, or $-N(R^8)(R^9)$;

(5) R^3 is hydrogen, halogen, alkyl, a carbocyclic ring, or a heterocyclic ring;

(6) R^4 is hydroxy;

(7) R^6 is hydrogen, halogen, nitro or $-N(R^8)(R^9)$; and

(8) X is a leaving group;

(B) and

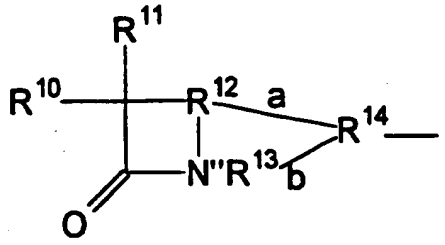
(1) when A^2 is $C(R^2)$, R^2 and R^3 may together comprise $-O-(CH_2)_n-O-$, where n is from 1 to 4;

(2) when A^3 is $C(R^5)$, R^4 and R^5 may together comprise a heterocyclic ring; and

(3) when A^1 is $C(R^7)$, R^7 and R^3 may together comprise a heterocyclic ring including A^1 and the carbon atom to which R^3 is bonded;

(C) and provided that one of R^1, R^3, or R^6 is a covalent bond to L^1;

(II) B has a structure according to Formula (II):



(II)

characterized in that

(A) R^{10} is hydrogen, halogen, alkyl, alkenyl, heteroalkyl, a carbocyclic ring, a heterocyclic ring, R^8-O-, R^8CH=N-, $(R^8)(R^9)$N-, R^{17}-C(=CHR^{20})-C(=O)NH-, R^{17}-C(=NO-R^{19})-C(=O)NH-, or R^{18}-$(CH_2)_m$-C(=O)NH-; where

(1) m is an integer from 0 to 9;

(2) R^{17} is hydrogen, alkyl, alkenyl, heteroalkyl, heteroalkenyl, a carbocyclic ring, or a heterocyclic ring;

(3) R^{18} is R^{17}, -Y^1, or -CH(Y^2)(R^{17});

(4) R^{19} is R^{17}, arylalkyl, heteroarylalkyl, -C(R^{22})-(R^{23})-COOH, -C(=O)O-R^{17}, or -C(=O)NH-R^{17}, where R^{22} and R^{23} are, independently, R^{17} r together comprise a carbocyclic ring or a heterocyclic ring including the carbon atom to which R^{22} and R^{23} are bonded;

(5) R^{20} is R^{19}, halogen, -Y^1, or -CH(Y^2)(R^{17});

(6) Y^1 is -C(=O)OR^{21}, -C(=O)R^{21}, -N(R^{24})R^{21}, -$S(O)_p$ R^{29}, or -OR^{29}; and Y^2 is Y^1 or -OH, -SH, or -SO_3H;

(a) p is an integer from 0 to 2;

(b) R^{24} is hydrogen; alkyl; alkenyl; heteroalkyl; heteroalkenyl; a carbocyclic ring; a heterocyclic ring; -SO_3H; -C(=O)R^{25}; or, when R^{18} is -CH(N(R^{24})R^{21})(R^{17}), R^{24} may comprise a moiety bonded to R^{21} to form a heterocyclic ring; and

(c) R^{25} is R^{17}, $-NH(R^{17})$, $-N(R^{17})(R^{26})$, $O(R^{26})$, or $S(R^{26})$; wher R^{26} is alkyl, alkenyl, a carbocyclic ring, a heterocyclic ring, or when R^{25} is $-N(R^{17})(R^{26})$, R^{26} may be a moiety bonded to R^{17} to form a heterocyclic ring; and

(7) R^{21} is R^{29} or hydrogen; where R^{29} is alkyl; alkenyl; arylalkyl; heteroalkyl; heteroalkenyl; heteroarylalkyl; a carbocyclic ring; a heterocyclic ring; or, when Y is $N(R^{24})R^{21}$ and R^{21} is R^{29}, R^{21} and R^{24} may together comprise a heterocyclic ring including the nitrogen atom to which R^{24} is bonded;

(B) R^{11} is hydrogen, halogen, alkoxy, or $R^{27}C(=O)NH-$, where R^{27} is hydrogen or alkyl;

(C) bond "a" is a single bond or is nil; and bond "b" is a single bond, a double bond, or is nil; except bond "a" and bond "b" are not both nil;

(D) R^{12} is $-C(R^{8})-$, or $-CH_2-R^{28}-$; where R^{28} is $-C(R^{8})-$, -O-, or -N-, and R^{28} is directly bonded to N" in Formula (II) to form a 5-membered ring;

except, if bond "a" is nil, then R^{12} is

(1) $-C(R^{8})(X^{1})-$, where

(a) X^{1} is $-R^{21}$; $-OR^{30}$; $-S(O)_rR^{30}$, where r is an integer from 0 to 2; $-OC(=O)R^{30}$; r $N(R^{30})R^{31}$; and

(b) R^{30} and R^{31} are, independently, alkyl, alkenyl, a carbocyclic ring or a heterocyclic ring; or R^{30} and R^{31} together comprise a heterocyclic ring including the nitrogen atom to which R^{30} and R^{31} are bonded; or

(2) $-CH_2-R^{32}-$; where R^{32} is $-C(R^{8})(R^{21})$, -O-, or $-NR^{8}$, and R^{32} is directly bonded to N" in Formula (II) to form a 5-membered ring;

(E) (1) if bond "b" is a single bond, R^{13} is $-CH(R^{33})$; or, $-C(O)NHSO_2-$, if bond "a" is nil; or $-C^{*}(R^{33})-$ if R^{14} contains a R^{36} moiety; where R^{33} is hydrogen or $COOR^{46}$, where R^{46} is hydrogen, alkyl or

alkenyl, and C* is linked to R^{36} to form a 3-membered ring;

(2) if bond "b" is a double bond, R^{13} is $-C(R^{33})=$; or

(3) if bond "b" is nil, R^{13} is hydrogen, $-SO_3H$, $-PO(OR^{34})OH$, $-C(O)NHSO_2N(R^{34})(R^{35})$, $-OSO_3H$, $-CH(R^{35})COOH$, or $-OCH(R^{34})-COOH$; where R^{34} is hydrogen, alkyl, alkenyl, a carbocyclic ring, or a heterocyclic ring; and R^{35} is hydrogen, alkyl, alkenyl, or $-NHR^8$; or, if R^{13} is $-C(O)NHSO_2N-(R^{34})(R^{35})$, R^{34} and R^{35} may together comprise a heterocyclic ring including the nitrogen to which R^{34} and R^{35} are bonded; and

(F) (1) if bond "a" or bond "b" is nil, then R^{14} is covalent bond;

(2) if bond "a" and "b" are single bonds, R^{14} is $-W-C'''=C(R^8)-R^{37}-$, or $-W-C'''(R^{36})-R^{37}-$; or

(3) if bond "a" is a single bond and bond "b" is a double bond, R^{14} is $-C(R^8)(R^{38})-W-C'''-R^{37}-$; $-W-C(R^8)-(R^{38})-C'''-R^{37}-$; or $-W-C'''-R^{37}-$;

(4) where

(a) W is O; $S(O)_s$, where s is an integer from 0 to 2; or $C(R^{38})$, where R^{38} is hydrogen, alkyl or alkoxy;

(b) R^{36} is hydrogen; alkyl; alkenyl; -COOH; or, if R^{13} is $-C^*(R^{33})$, R^{36} may be linked to C* to form a 3-membered carbocyclic ring;

(c) R^{37} is covalent bond, alkyl, alkenyl, a carbocyclic ring, or a heterocyclic ring; and

(d) C''' is directly bonded to R^{13} to form a 5- or 6-membered ring; and

(III) (A) L is $-C(=Z)-$; $-S(O)_v-$; $-N(R^{44})-$; $-N^+(R^{44})(R^{45})$; $-N(R^{44})-N(R^{44})-$; -O-; =N-; or a covalent bond; and L is bonded to L^3 and L^4; where

(1) Z is O, S, or $^+N(H)_2$;

(2) v is 0, 1 or 2;

(3) R^{44} is hydrogen, substituted or unsubstituted lower alkyl, aryl, acyl, hydroxy, alkoxy, aryloxy, or acyloxy; and

(4) R^{45} is hydrogen, unsubstituted r substituted lower alkyl, or substituted or unsubstituted aryl;

(B) L^1 is L^3 or $R^{15}L^3$; where

(1) when L is -C(=Z)-, L^3 is a covalent bond, oxygen, sulfur, or nitrogen; and when L is other than -C(=Z)-, L^3 is a covalent bond;

(2) R^{15} is alkyl, alkenyl, heteroalkyl, a heterocyclic ring, a carbocyclic ring, or R^{15} together with L^3 is a heteroalkyl or a heterocyclic ring; and

(3) L^1 is bonded to Q at the point of attachment of R^1, R^3 or R^6, whichever is a covalent bond;

(C) L^2 is L^4, $-X^2_t-R^{39}-L^4$, or $-X^3_t-R^{39}-L^4$; where

(1) when L is -C(=Z)-, L^4 is a covalent bond, oxygen, sulfur, or nitrogen; and when L is other than -C(=Z)-, L^4 is a covalent bond;

(2) X^2 is oxygen, or $S(O)_v$, where v is 0, 1, or 2;

(3) X^3 is nitrogen; $N(R^{40})$; $N^+(R^{41})(R^{42})$; or R^{43}-$N(R^{41})$; and is linked to R^{14} by a single or double bond; or, if R^{14} is covalent bond, X^3 is linked to B by a single or double bond; where

(a) R^{40} is R^8; $-OR^8$; or $-C(=O)R^8$;

(b) R^{41} and R^{42} are, independently, hydrogen; alkyl; alkenyl; carbocyclic rings; heterocyclic rings; or, if R^6 is $R^{16}X$, then R^{41} and R^{42} together with Q" may comprise a heterocyclic ring as R^{16};

(c) R^{43} is $N(R^{41})$, oxygen or sulfur;

(4) t is 0 or 1;

(5) R^{39} is alkyl, alkenyl, heteroalkyl, heteroalkenyl, a carbocyclic ring, or a heterocyclic ring; and

(6) (a) if bond "a" or bond "b" is nil, then L^2 is bonded directly to R^{12} or R^{13}; or

(b) if bond "a" and bond "b" are not nil, then L^2 is bonded to R^{14};

(D) provided that if L^1, L^2 and R^{37} is each a covalent bond, then L is not a covalent bond;

or a protected form, salt, ester, or solvate thereof.

13. The compound of Claim 12, characterized in that A^1 is nitrogen, A^2 is $C(R^2)$, and A^3 is $C(R^5)$ or, preferably, A^1 is $C(R^7)$, A^2 is $C(R^2)$, and A^3 is $C(R^5)$; R^1 is alkyl, aryl, cycloalkyl, or alkylamino; R^7 is hydrogen or halogen; and R^3 is a heterocyclic ring, preferably a substituted or unsubstituted pyrrolidine or a substituted or unsubstituted piperazine.

14. The compound of Claim 12, characterized in that

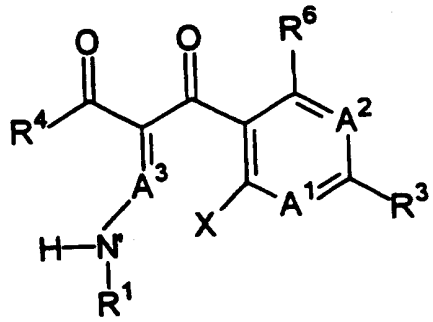
(a) R^3 is a covalent bond to L^1 or R^6 is a covalent bond to L^1;

(b) (i) L is -C(=Z)-, where Z is O, and L^3 is nitrogen; or

(ii) L is $-N(R^{44})-$, where R^{44} is hydrogen or unsubstituted or substituted lower alkyl; and

(c) R^{14} is $-W-C''-R^{37}-$ or $-W-C(R^8)(R^{38})-C'''-R^{37}-$; preferably W is $S(O)_s$, where s is 0; or W is $C(R^{38})$.

15. A process for making the compound of Claim 12, Claim 13, r Claim 14, the method comprising reacting a compound having a structure according to Formula (III)



(III)

characterized in that

(A) (1) A^1 is N or $C(R^7)$; where

(a) R^7 is hydrogen, hydroxy, alkoxy, nitro, cyano, halogen, alkyl, or $-N(R^8)(R^9)$, and

(b) R^8 and R^9 are, independently, hydrogen, alkyl, alkenyl, a carbocyclic ring, or a heterocyclic ring; or R^8 and R^9 together comprise a heterocyclic ring including the nitrogen to which they are bonded;

(2) A^2 is N or $C(R^2)$; where R^2 is hydr gen or halogen;

(3) A^3 is N or $C(R^5)$; where R^5 is hydrogen;

(4) R^1 is hydrogen, alkyl, a carbocyclic ring, a heterocyclic ring, alkoxy, hydroxy, alkenyl, arylalkyl, or -N(R^8)(R^9);

(5) R^3 is hydrogen, halogen, alkyl, a carbocyclic ring, or a heterocyclic ring;

(6) R^4 is hydroxy;

(7) R^6 is hydrogen, halogen, nitro or -N(R^8)(R^9); and

(8) X is a leaving group

(B) and

(1) when A^2 is C(R^2), R^2 and R^3 may together comprise -O-$(CH_2)_n$-O-, where n is from 1 to 4;

(2) when A^3 is C(R^5), R^4 and R^5 may together comprise a heterocyclic ring; and

(3) when A^1 is C(R^7), R^7 and R^3 may together comprise a heterocyclic ring including A^1 and the carbon at m to which R^3 is bonded;

or a salt or ester thereof;

with a lactam-containing compound having a structure according t Formula (II).

INTERNATIONAL SEARCH REPORT

Int. onal Application No
PCT/US 95/09649

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D499/00 C07D501/00 C07D463/00 C07D477/14 C07D477/20
C07D215/56 C07D499/88

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO,A,94 10163 (THE PROCTER & GAMBLE COMPANY) 11 May 1994 *Document* ---	1,10,11
A	EP,A,0 366 193 (NORWICH EATON PHARMACEUTICALS) 2 May 1990 cited in the application *Document* ---	1,10,11
A	EP,A,0 366 641 (NORWICH EATON PHARMACEUTICAL) 2 May 1990 cited in the application *Document* -----	1,10,11

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

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"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
14 N vember 1995	22.11.1995

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+ 31-70) 340-3016	Luyten, H

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INTERNATIONAL SEARCH REPORT

Information on patent family members

Int :onal Application No
PCT/US 95/09649

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